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Basic Organic Chemistry

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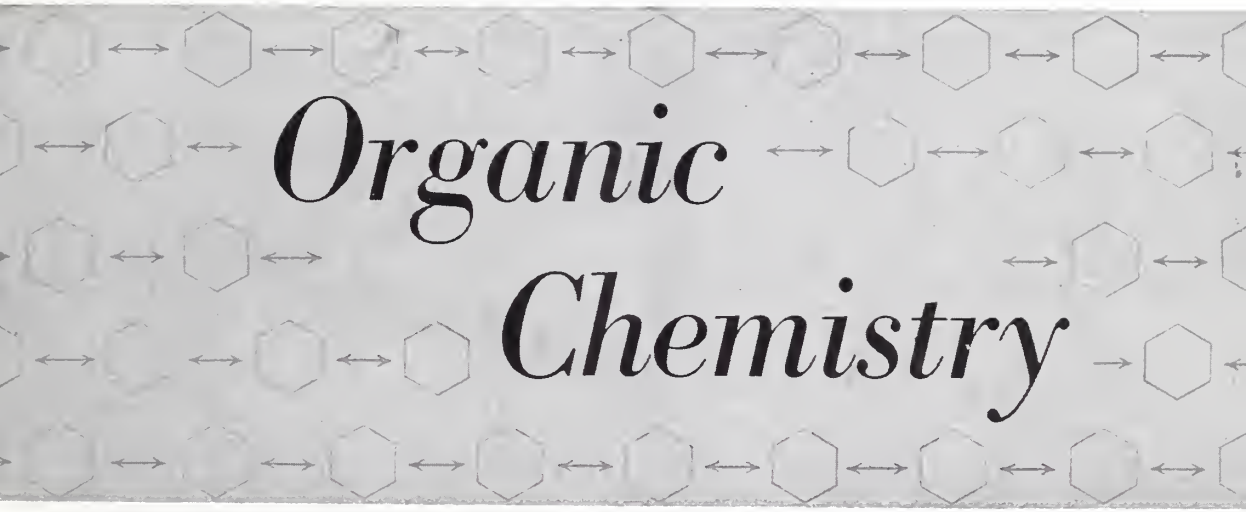
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Basic Organic Chemistry

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Basic



D. C. HEATH AND COMPANY Boston

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Preface

The objective of this book is to present the basic facts and theories of modern organic chemistry in an easily assimilable form and in a limited number of pages. The science has expanded so extensively that the best way of meeting the objective seemed to be to abandon the traditional organization into compound types in favor of organization of the bulk of the material into a series of topics. The topical presentation saves space by eliminating repetitions and detractive details, and achieves unification by centering attention on one topic at a time. Introduction of aromatic chemistry at an early stage not only contributes to further unification and condensation but also makes the scheduling of laboratory work more flexible.

The book is so organized that the requirements of courses of varying length for nonchemistry majors can be met by an appropriate selection of chapters. Thus a reasonably thorough coverage of basic aliphatic-aromatic chemistry is provided even though any or all of the following chapters are omitted: cycloalkanes, petroleum, synthesis, rearrangements, carbohydrates, lipids, proteins, polymers, dyes. In order that an instructor can easily shape his course according to the time available and the emphasis desired, the book is so organized that omission of any of the chapters mentioned will not detract from the usefulness of the chapters retained. Since the new presentation leaves more time for consideration of special topics of local or timely interest, the book may prove useful, with some supplementation, in courses for chemistry majors.

Numerous photographs of molecular models of three types will help the student grasp the meaning of projection formulas and understand the spatial arrangement of organic molecules. Other photographs illustrating successive stages in reactions and operational techniques are intended to enhance student interest and to emphasize the fact that the science is based

upon experimentation. Some of these scenes were photographed in color and made into slides for use in lecture demonstrations, and copies are available from Wilkens-Anderson Company.

Louis F. Fieser
Mary Fieser



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Basic Organic Chemistry

CHAPTER 1

NATURE OF ORGANIC COMPOUNDS

Types of Organic Chemicals. — The prominence of organic chemistry in various phases of modern life will be evident from a consideration of some of the types of known organic chemicals. Petroleum is a complicated mixture of compounds which contain hydrogen and carbon as the component elements and which therefore are called hydrocarbons. A few decades ago crude oil from wells was separated by distillation into a hydrocarbon fraction volatile enough for use as fuel in gasoline engines and a higher-boiling fraction of limited use in kerosene lamps. However, chemical research led to discovery of ways of transforming the original petroleum hydrocarbons into other hydrocarbons of vastly superior properties, and the refinery of today produces gasoline in double the original yield and of such improved quality as to meet the exacting requirements of a high-test fuel for efficient high compression-ratio automobile and aviation engines. Fuels tailored to the needs of Diesel and jet engines are made by processes of transformation and of synthesis. Petroleum technology has also made available chemicals that serve as intermediates to valuable products such as synthetic rubbers, plastics, and detergents. 1.1

Petroleum hydrocarbons

Motor fuels

The original hydrocarbons of petroleum are of a type exemplified by the simplest member, methane, which has the empirical formula CH_4, and which is the principal component of natural gas. Methane-type hydrocarbons are representative of one broad group of organic compounds. Another broad group includes compounds derived from the hydrocarbon benzene, of the formula C_6H_6. Benzene and related hydrocarbons result as by-products of the production from soft coal of the coke required for conversion of iron ore into iron. Heated to a high temperature, coal breaks down to a residue of coke, a gas useful for illumination (coal gas), and a fraction that distils and then condenses to a tar, coal tar. Redistillation of coal tar affords abundant 1.2

Coal tar hydrocarbons

supplies of aromatic hydrocarbons, including benzene (C_6H_6), naphthalene ($C_{10}H_8$), and anthracene ($C_{14}H_{10}$); some of them have pleasant aromas. These hydrocarbons are key starting materials for the production of synthetic dyes, plastics, insecticides (DDT), sulfa and other drugs.

1.3 *Plant products of technological use*

Plants afford many useful organic chemicals. Cotton is composed principally of cellulose, a carbohydrate useful as a textile fiber. Wood contains two main components, one of which is wood pulp, used for making paper. Wood pulp is a variety of cellulose that has considerable use because, by chemical transformations, it is convertible into artificial silks, guncotton, automobile lacquers, and plastics. Certain trees, shrubs, flowers, and fruits contain organic chemicals of value as plasticizers (camphor, for celluloid), perfumes, flavors, and paint ingredients (turpentine). These products are isolated either by extraction with an organic solvent or by distillation with steam. Synthetic camphor made from oil of turpentine is produced at a cost less than that of natural camphor from the native Formosan tree. Specific rare plants are worked up for isolation of very small amounts of substances of inestimable value in medicine, for example, digitalis from the purple foxglove, used for treatment of heart diseases, and morphine from the opium poppy, used for alleviation of excruciating pain (terminal cancer cases).

Medicinal plant products

1.4 *Constituents of foods*

The three major constituents of foods are carbohydrates, fats, and proteins; the first two are made up of C, H, and O, and proteins contain the same three elements and also N and S. Carbohydrates edible to man include sugars, which are water-soluble substances, and starch. Starch is made up of chains of multiple sugar units strung together to form giant molecules, but these are broken down in the body to sugar molecules which are easily assimilated. Cellulose contains similar but more stable giant molecules and is not digested by man; the cow has a special alimentary tract capable of digesting even cellulose. Fats of the diet are derived from both animal and plant sources, for example, beef fat, bacon fat, olive oil. Very abundant oils, such as peanut oil, whale oil, and coconut oil, are used for manufacture of soap, cooking grease, cosmetics, and surface-active agents (detergents, wetting agents). Proteins of the diet are also of both plant and animal origin. Lean meat and eggs are rich in proteins, as are cereals.

1.5 *Constituents of the body*

The main organic chemicals of the animal body are likewise carbohydrates, fats, and proteins; but these components, although derived from the diet, are modified to meet the requirements of the new organism. Study of the structure, properties, and synthesis of these compounds is part of the science of organic chemistry; biochemistry

is concerned with the dynamic functioning of the substances in the body, that is, the pathways by which they are formed (biosynthesis) and utilized for energy (metabolism). In addition to these main organic chemical constituents, the body contains tiny amounts of compounds necessary for health known as hormones (Greek *hormōn*, exciting). These are secreted by specific glands and often exert a regulatory or stimulating effect at a site remote from that of origin. Thus hormones of one type are produced in the pituitary gland of the brain and carried in the blood stream to the gonads, or sexual glands, where they stimulate production of the sex hormones, which are of an entirely different chemical type. Other hormones arise in the adrenal gland, adjacent to the kidneys, in the thyroid gland of the neck, and in the pancreas, an abdominal gland called sweetbread when used as food.

Hormones

1.6

Improper functioning of one of these glands results in inadequate production of an essential hormone and leads to a specific disease. If the hormone is known and if it is available for use in medicine, administration of the appropriate hormone to a person suffering from a glandular-involved, or endocrine, disease may cure or alleviate the disease. Thus the disease diabetes results from inability of the pancreas to produce adequate amounts of the hormone insulin. Insulin is a giant-molecule protein which chemists have not yet been able to produce by synthesis. However, insulin isolated by chemical processing of sheep or ox pancreas is of established value for treatment of diabetes. The adrenal hormone cortisone has an alleviating effect on a particularly crippling form of arthritis, but the amount that can be isolated from 1000 lbs. of hog or beef adrenal glands would suffice only for treatment of a single patient for one or two weeks. Synthetic cortisone, manufactured by highly ingenious chemical reactions, enables previously bed-ridden patients to walk, work, and enjoy life again.

Hormonal treatment of endocrine diseases

1.7

Another group of organic compounds essential to the proper functioning of the animal organism are vitamins, derived from foods. Like hormones, vitamins are required, often in extremely small amounts, for normal functioning of the body and hence for preservation of health. Vitamins are essential regulatory substances comparable to hormones, and a dietary deficiency in a specific vitamin can lead to a specific disease, for example, scurvy, beri-beri, or softening of the bones (rickets) in children and in chicks. Vitamins of the human diet are products synthesized by plants, or present in milk, butter, eggs, or fish oils, and which are not available in adequate amounts by biosynthesis.

Vitamins

Deficiency diseases

1.8

In civilized countries of the modern world some of the essential

vitamin factors of vegetable origin are adequately supplied by orange juice, green vegetables, and cereals. Other required vitamins are present in the two great staple grain foods: wheat in the western world, and rice in the Orient. However, the vitamins are present in a brown layer of bran that coats the grains. Since most people prefer white bread to brown, the vitamin-containing bran is largely eliminated from wheat grains in the milling process for production of white flour. The vitamins native to rice are similarly lost in the course of washing to produce a white, nonsticky grain (polished rice).

Enrichment of foods

To make up for the loss in original nutrient value, flour is now enriched in most states by addition of vitamins according to recommendations of the Food and Nutrition Board of the National Research Council. The vitamins thiamine, riboflavin, and niacin are added to bring the nutrient level up to what it had been originally. In some of the southern states vitamin-enriched rice and cornmeal are the standard grain foods. Margarine is enriched with vitamins A and D to make it the nutrient equivalent of butter. Both evaporated milk for infant feeding and poultry feed are enriched with vitamin D for protection against rickets.

1.9 **Function of the Chemist.** — Modification of petroleum hydrocarbons for production of high-quality motor fuels and synthetic intermediates required knowledge of the structures of the compounds, that is, the number of carbon and hydrogen atoms present and the way in which the atoms are joined together in the molecules. Development of methods for synthesis of dyes and drugs from coal tar hydrocarbons was dependent upon determination of the structure of the parent hydrocarbon benzene, C_6H_6. Production of synthetic rubbers was based upon investigations of the structure of natural rubber. Hormones and vitamins were made available in amounts adequate to safeguard health only after teams of chemists, by years of research, had achieved isolation of the substances in pure form, elucidated their structures, and worked out efficient methods for their synthesis.

1.10 **Nature of the Course.** — A short course in organic chemistry can hardly cover many details of all the achievements of the science summarized above, but it can provide an understanding of the basic principles of modern organic chemistry sufficient for an appreciation of at least some of the major applications to technology and medicine. The principles hold the key to the applications, and are in themselves very interesting. Indeed organic chemistry is fascinating as a pure science, quite apart from its usefulness.

1.11 The subject is not easy, and students who, in the early stages, gain the impression that it is easy are liable to be mistaken. Concepts

which appear simple and understandable when explained may present more difficulty when one attempts to state and apply the reasoning. It takes some time before a beginner is able to see flaws in his own answers and formulations. Studying in pairs is often effective, with students alternating in asking and answering questions, for the questioner may sometimes see flaws in another's answers which he would not see in his own. It is imperative that study be regular, for the subject develops in a logical order and each new topic is based on material preceding it. Each assignment must be studied as it comes, for otherwise there is danger of one's becoming hopelessly lost.

Practice in writing formulas should be an invariable rule of study. 1.12
Writing a set of formulas or reactions a few times, with critical review to make sure they are correct, makes the material rememberable with greater ease and accuracy than if the same time were spent looking at formulas in a book.

Compounds of Carbon. — Organic chemistry actually is better 1.13
defined as the chemistry of carbon compounds. The designation organic was applied in an early era of the science — over a century ago — when the only carbon compounds known other than simple substances such as CO_2, $CaCO_3$, and KCN were all natural products arising in either plants or animals, for example, sugar ($C_{12}H_{22}O_{11}$) from sugar cane, urea (CH_4ON_2) from urine, the dye alizarin ($C_{14}H_8O_4$) from the root of the madder plant. Today hundreds of thousands of carbon compounds are described as organic compounds even though the number isolated from plant and animal tissues is far exceeded by the number created by chemists by ingenious techniques of synthesis.

Definition of organic chemistry

The element carbon is distinguished from all the other elements 1.14
by its ability to form a multiplicity of compounds. The reason for this unique character is that carbon occupies a special position in the periodic table, reproduced in part in Table 1.1, since it is at the top and center. The noble-gas or zero-group elements, placed at both

Unique character of carbon

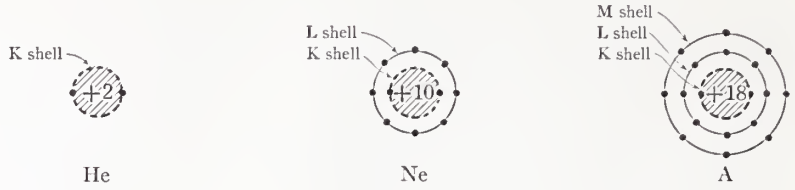
Table 1.1. Periodic Table (atomic numbers under symbols)

O	I	II	III	IV	V	VI	VII	O
	H 1							
He 2	Li 3	Be 4	B 5	C 6	N 7	O 8	F 9	Ne 10
Ne 10	Na 11	Mg 12	Al 13	Si 14	P 15	S 16	Cl 17	A 18

the left and the right side of the table, are characterized by the extreme stability of their electronic structures. Helium (He), the ele-

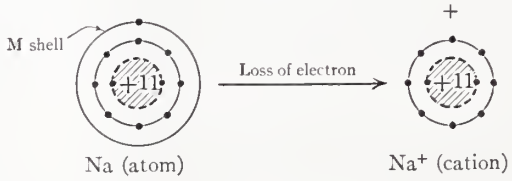
ment of atomic number 2, has a stable 2-electron shell, or K shell, surrounding the nucleus and balancing the charge of +2. In neon

Noble gases



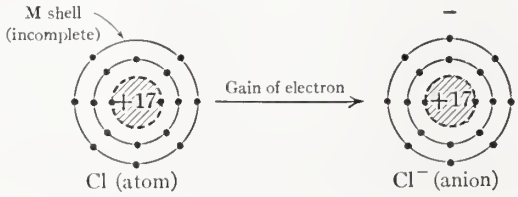
(Ne) the K shell is surrounded by an equally stable L shell of eight electrons. Argon (A) has the same K and L shells, and a further M shell that is again a stable octet. These elements form no compounds with other elements or with themselves; they have no valence, or combining capacity (Latin *valentia*, vigor, or capacity). The electrons in the outermost shells of the noble gas elements are not available for any kind of chemical interaction, and it is thus seen that a shell of either two or eight electrons is a particularly stable configuration. Sodium has K and L shells like neon and, in addition, the beginning of an M shell containing one lone electron. When a sodium atom loses this outer electron to form a positively charged ion, a cation, the peeling off of the M shell uncovers an electronic configuration which is precisely that of neon. Because of the special stability of this structure, sodium is prone to lose its valence electron.

Electron donor



Sodium is thus an electron donor. Since in the original atom the total complement of negative electrons balances the positive charge of the nucleus, loss of an electron results in formation of a positively charged particle, a cation. Sodium is thus an electropositive element. Chlorine is just the opposite. It has an outer M shell of seven electrons, or just one short of an octet, and hence it tends to gain an

Electron acceptor



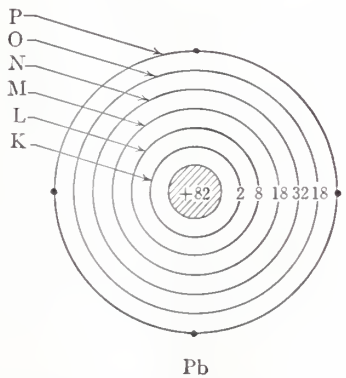
electron and thus acquire the stable electronic configuration of argon. Chlorine is thus an electron acceptor, or electronegative element. Sodium and chlorine therefore form the stable compound sodium chloride by a process of electron transfer whereby each element forms an ion of stable noble-gas electronic configuration. The product, sodium chloride, is an ionic compound made of oppositely charged parts.



Electron transfer

Carbon, with four valence electrons, has no more tendency to lose than to gain electrons and *tends to resist acquisition of either a positive* 1.15



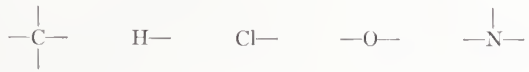


or negative charge. Lead, a higher member of group IV, also has four external electrons, but these are so far removed from the atomic nucleus because of the intervening electron shells that the attraction by the nucleus is weak enough to permit electron transfer to form Pb^{++}. In carbon, the valence electrons are so close to the nucleus that the attractive force opposes charge separation.

Structure. — If carbon is neither an electron donor nor an electron acceptor, some process other than electron transfer must be involved in the formation of carbon compounds such as the following: 1.16

Methane, CH_4	Carbon tetrachloride, CCl_4
Ethane, C_2H_6	Carbon dioxide, CO_2
Propane, C_3H_8	Hydrogen cyanide, HCN

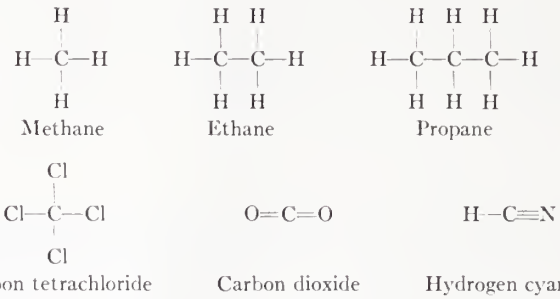
In 1859, long before the atom was known to contain a positive nucleus surrounded by electrons, the German chemist August Kekulé deduced that the carbon in all these compounds must have a valence of four and that it is joined to other elements by four chemical bonds, represented by lines. Hydrogen and chlorine, of valence 1, have one such



Valence bonds

bond each, oxygen has two, and trivalent nitrogen has three. Carbon can thus join with four hydrogens to form the molecule of methane. In ethane two carbon atoms are bonded by utilization of one bond of

Kekulé formulas

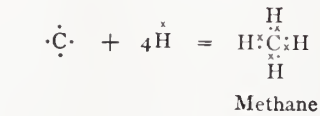


each, and each is further bonded to three hydrogen atoms. A third carbon in the chain gives the structure of propane, which indeed corresponds to the formula C_3H_8 given above. Carbon tetrachloride is similar in structure to methane. Carbon dioxide has two double bonds, which utilize the four valences of carbon and the two valences of each oxygen. In hydrogen cyanide carbon is singly bonded to hydrogen and triply bonded to trivalent nitrogen. Double and triple bonds are possible also between carbon atoms, as shown in the formulas for ethylene and acetylene; in each case, the number of



lines or bonds extending to each carbon atom is four, the valence of carbon.

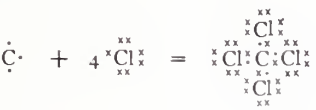
1.17 Kekulé's concept of structure proved to be widely applicable and stimulated rapid development of the science. However, the meaning of the Kekulé bond in terms of physical reality remained obscure until 1916. In that year G. N. Lewis, professor of physical chemistry at the University of California, introduced the concept of an electronic bond formed by a process of electron sharing. If each of four hydrogen atoms shares its electron (cross) with one of the four valence electrons of carbon (dots), a stable compound results, methane, in which each hydrogen is associated with two electrons, as in helium,



and the carbon atom is surrounded by a stable octet, as in neon and argon. No electron transfer is involved, and hence methane is non-

ionic. The four electrons of carbon can equally well fill the gaps in the electron septets of four chlorine atoms to give another typically nonionic compound, carbon tetrachloride, in which each of the five atoms concerned is surrounded by an electron octet. Electron sharing

Electron sharing



Carbon tetrachloride

between two or more carbons is also possible, as in the combination of two carbon and six hydrogen atoms to form ethane, and as in propane.



Ethane Propane

A bond between atoms consisting of a pair of shared electrons is called a covalent bond. In the hydrocarbon ethane two carbons are linked by a covalent bond, and each carbon is covalently bonded to three hydrogens. The sharing of electrons to form a covalent bond involves no appearance of an ionic charge, and hence organic compounds are nonionic. Thus CCl_4 gives no precipitate with silver nitrate solution, as does Na^+Cl^-.

Covalent bond

The Lewis formulas for the compounds cited give the same general concept of structure as the Kekulé formulas, and it is evident that the Kekulé bond can now be defined as a pair of shared electrons. Kekulé's double bond is then two pairs of shared electrons, as in ethylene,

1.18

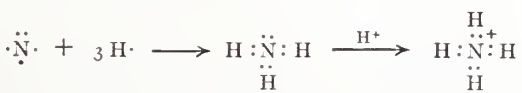


Ethylene Acetylene

and the triple bond of acetylene consists of three shared electron pairs. Each carbon atom of acetylene has associated with it eight electrons: its original four electrons plus one shared with hydrogen and three shared with the second carbon.

In the case of compounds containing nitrogen or oxygen, electronic formulas disclose a property not evident from Kekulé formulas. Nitrogen, with five valence electrons, forms with hydrogen the covalently bonded compound ammonia:

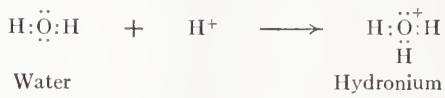
1.19



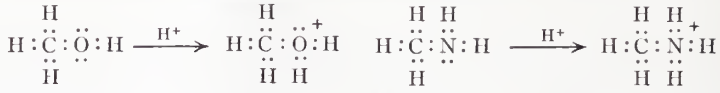
Ammonia Ammonium ion

Unshared electrons

In ammonia, unlike methane, the octet surrounding the central atom includes a pair of unshared electrons, and hence ammonia can combine with a proton (hydrogen ion) by sharing the extra electron pair with hydrogen to give an ammonium ion, which carries the charge derived from the proton. Oxygen (6 electrons) forms compounds containing two pairs of unshared electrons, for example water, and water



likewise combines with a proton to form a hydrated proton or hydronium ion, and this ion or a hydrate of it is present in an aqueous solution of a mineral acid. Methyl alcohol likewise can combine with a proton by utilization of its unshared electrons. Thus the



oxygen is basic, although not so strongly basic as the nitrogen in ammonia or in methylamine, and oxonium salts are hence not so stable as ammonium salts. Cations such as those from methyl alcohol, however, exist in solution and participate in certain reactions of alcohols. It should be noted in passing that methyl alcohol and methylamine can be regarded as derived from methane by replacement of one hydrogen by OH, a hydroxyl group, or by NH_2, an amino group. They can also be regarded as derived from water and from ammonia, respectively, by replacement of one hydrogen by the methyl group.

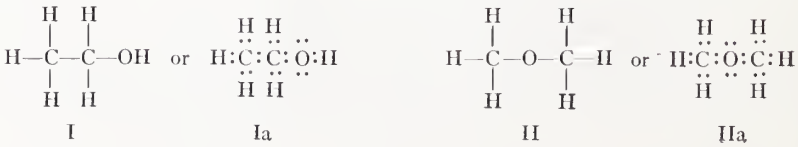
1.20 Kekulé formulas, because of their simplicity, are often used in place of electronic formulas but with the electronic counterpart implied. Formulas are also abbreviated further by grouping elements and leaving out some or all Kekulé bonds, as:

Abbreviations

CH_4	$CH_3CH_2CH_3$	$CH_2{=}CH_2$	$HC{\equiv}CH$	CH_3OH
Methane	Propane	Ethylene	Acetylene	Methyl alcohol

1.21 **Kekulé Structural Theory.** — Structures are easily derivable for the compounds thus far considered because in each case only one structure, or arrangement of atoms, is possible. However, the empirical formula C_2H_6O corresponds to two possible structural formulas, I (or Ia) and II (or IIa). The electronic formulations show that both

Problem of structure



structures fulfill electronic requirements for stability. In I the basic structural unit is carbon–carbon–oxygen, and in II it is carbon–oxygen–carbon. Two substances of the formula C_2H_6O do indeed exist and are defined as **isomers,** meaning that they are built of the same component parts (Gr. *isos*, same; *meros*, part). How can they be distinguished? Which isomer has the structure I, and which II?

Isomers

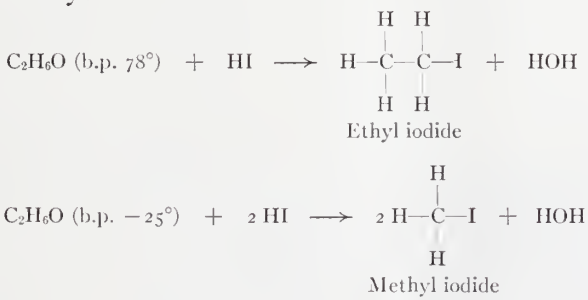
Kekulé introduced in 1859 a basic principle for determination of structure which has been used ever since. This involves consideration of all possible structures corresponding to the empirical formula and selection of the one which alone is consistent with the properties and reactions of the compound and (or) with methods for its synthesis. The two isomers of the formula C_2H_6O, mentioned above, can be distinguished by their boiling points, 78° and −25°, and the problem is to identify each isomer with the correct structural formula, I or II. Experiment shows that the isomers react in different ways with hydriodic acid, namely:

1.22

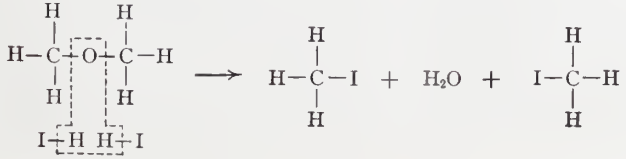
Principle of structure determination

Example

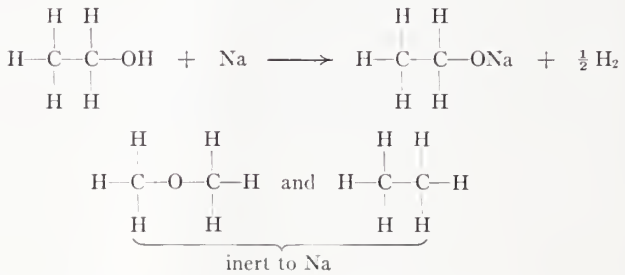
Chemical properties



The higher boiling isomer reacts with one equivalent of acid to give a molecule each of water and C_2H_5I, for which only one formula is possible, that of ethyl iodide. Iodine, entering the molecule, displaces the hydroxyl group (OH), which combines with H of HI to form HOH. Structure I contains a hydroxyl group whereas II does not, and hence the observation is consistent only with the structure I for the isomer b.p. 78°. The evidence would be incomplete if the behavior of the isomer b.p. −25° were not considered as well. This isomer reacts with hydriodic acid at a higher temperature, consumes two moles of reagent, and gives two moles of methyl iodide and water. This behavior is consistent alone with formula II, in which two methyl groups are joined through an intervening oxygen. When the central oxygen is abstracted by two hydrogen atoms, the molecule is disrupted and each methyl group left free to combine with iodine:



Both reactions with hydriodic acid thus lead to the conclusion that the isomer b.p. 78° is ethyl alcohol, CH_3CH_2OH (I) and the isomer b.p. −25° dimethyl ether, CH_3OCH_3 (II). Confirmatory evidence is that ethyl alcohol reacts with metallic sodium with displacement of one hydrogen by sodium, whereas dimethyl ether is inert to the metal. In structure I one hydrogen is attached to oxygen and therefore is different from the other five, which are linked to carbon; in structure II all six hydrogens are carbon-bonded, like those of ethane, which is inert to sodium. Hence the differing behavior is consistent with the formulas:



1.23 *Confirmation by synthesis*

Structures assigned from chemical properties and reactions can often be confirmed by synthesis. In the present example, ethyl alcohol can be synthesized as in (1) by the action of silver hydroxide on ethyl iodide; the reaction is just the reverse of that mentioned

1. $CH_3CH_2I + AgOH \longrightarrow CH_3CH_2OH + Ag^+I^-$
2. $CH_3CH_2OH + HI \longrightarrow CH_3CH_2I + H_2O$
3. $CH_3OH + Na \longrightarrow CH_3ONa + \frac{1}{2}H_2$
4. $CH_3I + NaOCH_3 \longrightarrow CH_3OCH_3 + Na^+I^-$

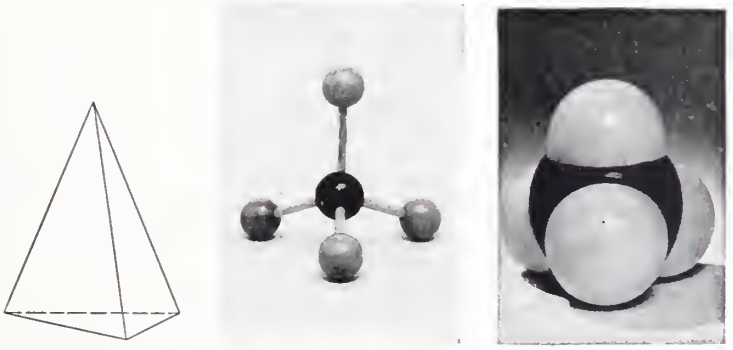
above and reformulated in (2). The structure of ethyl alcohol is established unambiguously by this synthesis because only one structure is possible for CH_3CH_2I and there can be no doubt that OH of AgOH replaces the iodine atom. Dimethyl ether can be synthesized by the equally unequivocal two-step process involving reactions (3) and (4). Reaction (3) is analogous to the reaction of ethyl alcohol with sodium cited above. Reaction (4) is analogous to reaction (1); in each case an organic halide reacts with a metal-containing compound, and the driving force is the tendency of the metal and the halogen to split out to form an ionic salt, Ag^+I^- and Na^+I^-.

1.24 **Possible and Impossible Formulas.** — Since the valence numbers of carbon and oxygen are both even, compounds containing only C, H, and O, as well as hydrocarbons, invariably contain an even number

of hydrogen atoms. Thus formulas such as C_6H_{11} and $C_7H_7O_5$ are at once recognized as fallacious. Compounds of C, H, and S, or C, H, O, and S, likewise must have an even number of hydrogens; for example, $C_{27}H_{46}O_3S_2$ is possible, $C_{27}H_{47}O_3S_2$ is impossible. Since nitrogen has a valence of three in typical organic substances, compounds containing C, H, O, and one N always have an odd number of hydrogens; if two nitrogens are present, the number of hydrogens is even. In mono and di halogen compounds containing C, H, O, and S, the number of hydrogens is odd and even, respectively.

Arrangement of Atoms in Space. — What is the shape of the methane molecule? Is it flat, with all five atoms in a plane? Is it spherical? This question was answered independently in 1873 by two young chemists, Jacobus H. van't Hoff, in Holland, and Joseph A. Le Bel in France, and their inductive inferences were later abundantly confirmed by chemical and physical evidence. The methane molecule is three-dimensional and symmetrical, with carbon at the center and the four hydrogens attached symmetrically and each equidistant from the others. Thus the carbon atom is tetrahedral, as in (a); the four electron pairs of an octet tend to take up positions in space at the corners of a regular tetrahedron. In methane the carbon is at the

1.25



(a) (b) (c)

Tetrahedral configuration of carbon

center of the tetrahedron with its four valences directed toward the corners. The arrangement is shown schematically in the model (b), in which the central carbon is black and the attached hydrogens gray. This model shows that the angle between any pair of valence bonds corresponds to the tetrahedral angle of 109° 28′, but the balls, of a purely arbitrary size, do not reflect the relative size of carbon and hydrogen atoms. The Stuart model (c) gives an accurate conception of the actual shape of the methane molecule because the atoms are represented by spheres of appropriate relative diameters and facings on a scale proportional to the actual interatomic distances. Carbon (black) is larger than hydrogen (white), and the merging of

atoms to form the molecule is attended with some compression or flattening of the original spheres.

1.26 Classification of Types. — Methyl iodide, CH_3I, and ethyl iodide, C_2H_5I, are representatives of a group of compounds that includes the bromides (CH_3Br, C_2H_5Br), the chlorides, and the fluorides, and also similar halides derived from propane (C_3H_8) and hydrocarbons still higher in the series. Early chemists saw a formal analogy between alkali halides, such as NaCl, KBr, KI, and organic halides of the type CH_3Cl, C_2H_5Br, and C_2H_5I, and named the latter "alkali-like" halides or alkyl (alkali + yl) halides. The name has been retained, and the symbol RX is used as a general formula for any alkyl halide; X stands for any halogen (F, Cl, Br, I), and R represents any hydrocarbon group such as methyl, ethyl, propyl, or other alkyl group. If RX represents any alkyl halide, then ROH represents any alcohol, for example, methyl alcohol, CH_3OH, or ethyl alcohol, C_2H_5OH. The reaction of ethyl alcohol with hydriodic acid (1.22) is an example of a reaction which can be formulated in general terms as follows:

Alkyl groups

Type formulas

$$\underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX} \longrightarrow \underset{\text{Alkyl halide}}{RX} + H_2O$$

1.27 Methane and ethane can be thought of as combinations of the methyl and ethyl group with hydrogen, CH_3—H and C_2H_5—H, and the general formula for such a hydrocarbon is RH, whence the generic name (class name) **alkane.** Ethylene and acetylene are the common names of the first members of series of hydrocarbons characterized by having double and triple bonds, respectively, and hence, in a systematic nomenclature worked out at an international congress at Geneva in 1890, these series are designated **alkenes** (from ethylene) and **alkynes** (from acetylene).

Geneva names

1.28 A generalized formula of another type is derived as follows. The simplest alkane is methane, CH_4, and the next member is ethane, C_2H_6, and in each case the number of hydrogen atoms is twice the number of carbon atoms plus 2. If n stands for the number of carbons, the number of hydrogens is (2n + 2), and hence the general formula for these hydrocarbons and for all other alkanes is C_nH_{2n+2}. This fits the empirical formulas of propane (C_3H_8) and of butane (C_4H_{10}), which are described as the next two members of the homologous series of alkanes. Succeeding homologs differ in composition by one carbon and two hydrogen atoms, or by the increment of CH_2, a methylene group. The alkane having 10 carbon atoms, or the C_{10}-alkane, is a higher homolog of methane, and the formula, easily derivable from the type formula, is $C_{10}H_{22}$. Ethylene, $CH_2{=}CH_2$, has two hydrogens less than ethane, and any alkene must have two hydrogens less than

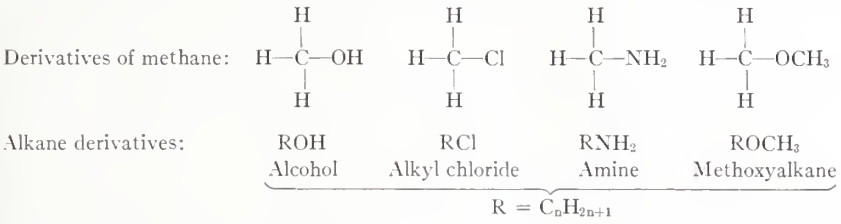
Alkanes, C_nH_{2n+2}

the alkane of the same number of carbon atoms; hence the type for alkenes in general is C_nH_{2n}. Acetylene, C_2H_2, and homologous acetylenes, such as C_3H_4, C_4H_6, conform to the type C_nH_{2n-2}.

Alkenes, C_nH_{2n}
Alkynes, C_nH_{2n-2}

The compounds listed in the first row below can be imagined as derived from methane by replacement of one of the four hydrogens by one of the groups: —OH (hydroxyl group), —Cl, —NH_2 (amino

1.29



group), —OCH_3 (methoxyl group). Each compound is the first member of a homologous series of the type listed in the second row. Since the alkyl group R has one hydrogen less than the corresponding alkane, the general formula for it is C_nH_{2n+1}.

The compound types listed and a few additional ones belong to one of two broad groups of organic compounds. Compounds of the first group, identifiable as being derived from methane or other alkane, are called aliphatic. The word is derived from the Greek word *aleiphatos*, meaning fat, and the connection is that animal and vegetable fats, with which early chemists were familiar, are made up of molecules in which large alkyl groups such as $C_{15}H_{31}$— and $C_{17}H_{35}$— are the predominating characteristics. All other compounds which have an alkane part, or which are alkanes, alkenes, and alkynes, are now classified as aliphatic. The second group is composed of compounds derived from or related to benzene, C_6H_6. It includes, for example, compounds analogous to the derivatives of methane listed above; the corresponding derivatives of benzene are C_6H_5OH, C_6H_5Cl, $C_6H_5NH_2$, and $C_6H_5OCH_3$. Because the first-known derivatives of benzene were natural products extracted from balsams and impressed the discoverers because of their fragrant aromas, the group as a whole came to be known as aromatic compounds.

1.30

Aliphatic series

Aromatic series

The group C_6H_5— in the above compounds is called a phenyl group; the corresponding group derived from naphthalene, $C_{10}H_8$, is called a naphthyl group, $C_{10}H_7$—. The general name for groups of this type is aryl, from aromatic, and the symbol is Ar. Thus ArCl is an aryl chloride, just as RCl is an alkyl chloride.

1.31

SUMMARY

Types of organic compounds. Petroleum a mixture of hydrocarbons. Transformation to other hydrocarbons of superior properties for use in gasoline engines, Diesel and jet engines, or for conversion to synthetic rubbers, plastics, detergents.

Hydrocarbons from coal tar: benzene, naphthalene, anthracene. Use for production of dyes, plastics, insecticides, sulfa drugs, etc.

Plant products. Cotton is almost pure cellulose. Wood pulp, largely cellulose, is convertible by chemical transformations into artificial silks, guncotton, automobile lacquers, plastics. Trees, shrubs, flowers, fruits afford chemicals of value as plasticizers, perfumes, flavors, paint ingredients. Valuable medicinals (e.g., digitalis, for heart therapy; morphine, for alleviation of pain) isolated from specific plants.

Constituents of foods. Carbohydrates (C, H, O): sugar, starch. Fats (C, H, O), from both animals and plants (beef fat, bacon fat, olive oil); use of abundant fats for manufactured products. Proteins (C, H, O, N, S) of the diet are of both animal and plant origin.

Constituents of the body: carbohydrates, fats, and proteins in modified form. Also hormones, which are regulatory compounds produced in specific glands. Hormonal treatment of glandular-involved diseases (insulin for diabetes, cortisone for arthritis).

Vitamins in vegetables, orange juice, cereals required for preservation of health. Deficiency diseases: scurvy, beri-beri, rickets. Enrichment of flour with the vitamins lost in removal of bran to produce white flour. Enrichment of margarine and milk.

Compounds of Carbon

Stability of noble gases with an outer shell of either 2 electrons (He) or 8 electrons (Ne, A). Sodium, by donation of its lone valence electron, forms an ion with a stable electron octet. Chlorine, with 7 valence electrons, tends to acquire one more electron to form an octet. Hence donor and acceptor elements form stable, ionic Na^+Cl^- by electron transfer. Carbon (top center of periodic table) tends neither to lose its four electrons nor to gain four more. The valence electrons are closer to the nucleus than those of lead, and the attractive force better opposes charge separation. Electron transfer thus not involved in formation of carbon compounds (called organic since first ones known were derived from organisms).

Kekulé concept of structure (1859), with lines to represent chemical bonds. Structures of methane (CH_4), ethane (C_2H_6), propane (C_3H_8), CCl_4, CO_2, HCN, ethylene (double bond), acetylene (triple bond).

G. N. Lewis concept (1916) of the formation of stable compounds by electron sharing. Covalent bond a pair of shared electrons. Electronic formulas for CH_4, CCl_4, ethane, propane, ethylene (two pairs of shared electrons), acetylene (three electron pairs). Ammonia and water, with unshared electrons on N or O, combine with a proton (hydrogen ion) to form cations, NH_4^+, H_3O^+. Same true of methylamine and methyl alcohol.

Kekulé bond now defined as a pair of shared electrons. Kekulé formulas used because of simplicity but with electronic counterpart implied.

Kekulé Structural Theory

Kekulé principle for determination of structure: consider all possible structural formulas and select the one that accords with the chemical properties and (or) synthesis. Example: two isomers of the formula C_2H_6O identified as CH_3CH_2OH (ethyl alcohol) and CH_3OCH_3 (dimethyl ether) by results of reactions with HI and with Na; confirmation by synthesis of both substances.

Principle of valence balance: even number of hydrogen atoms required for compounds of C, H; C, H, O; C, H, S; C, H, O, S; C, H, N_2; C, H, O, N_2; C, H, O, N_4; C, H, Cl_2; odd numbers for compounds of C, H, N; C, H, O, N; C, H, O, N_3; C, H, Cl; C, H, O, Cl_3.

Arrangement of Atoms in Space

van't Hoff-Le Bel theory of tetrahedral nature of carbon. Representation of methane with ball-and-stick and with Stuart models. Stuart model shows actual shape.

Geneva nomenclature; alkyl group, R (methyl, ethyl); alkyl halide, RX (methyl chloride, bromide, or iodide, an ethyl halide); alkane, RH (methane, ethane. propane); alkene (double bond, as in ethylene); alkyne (triple bond as in acetylene).

Type formulas. Methane (CH_4), ethane (C_2H_6), propane (C_3H_8), and all higher alkanes conform to the general formula C_nH_{2n+2}. Members of such a series differing by CH_2 described as homologs. Alkenes: C_nH_{2n}. Alkynes: C_nH_{2n-2}. Replacement of one H of an alkane by OH, Cl, NH_2, OCH_3 gives an alcohol, ROH, an alkyl chloride, RCl, an alkyl amine, RNH_2, or a methoxyalkane, $ROCH_3$. Type formula of the R group: C_nH_{2n+1}.

Aliphatic compounds: alkanes, alkenes, alkynes, and derived compounds (name derived from the fact that some of the early recognized members are constituents of fats). Aromatic compounds: derived from or related to benzene (origin of name: some of the first-known members were natural products of fragrant aroma). Symbol for a phenyl, naphthyl, or other aromatic group: Ar (aryl).

PROBLEMS

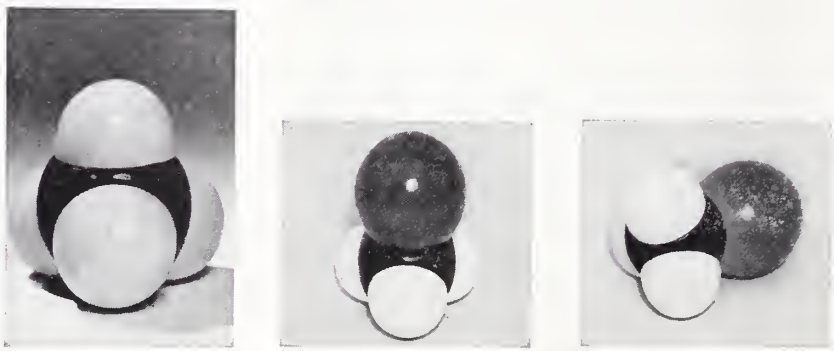
1. Write Kekulé formulas for hydrazine, N_2H_4 (trivalent N), formic acid, CH_2O_2; oxalic acid, $C_2H_2O_4$.
2. Write electronic formulas for $CHBr_3$, CO_2, HCN.
3. There are two isomers of the formula $C_2H_4Br_2$ and two of the formula $C_2H_3Br_3$. Write the four structural formulas.
4. The synthesis of ethyl alcohol from C_2H_5I and AgOH proves its structure. Would the synthesis of a propyl alcohol from C_3H_7I prove its structure?
5. Write structural formulas for all possible isomers of the formula C_3H_8O. One isomer is inert to sodium, and when heated with HI it yields a mixture of methyl iodide and ethyl iodide. What is its structure?
6. Write formulas for all possible monochloro derivatives of *n*-hexane, $CH_3CH_2CH_2CH_2CH_2CH_3$.
7. Which of the following formulas represent possible compounds and which are false: $C_{10}H_{22}O$, $C_{20}H_{41}$, $C_{14}H_8O_4$, $C_{21}H_{31}O_3$, $C_{21}H_{31}O_3N$, $C_8H_{14}ON$, $C_{20}H_{32}OSN_2$, $C_{10}H_{20}Br_3$?

CHAPTER 2

STRUCTURES OF ALIPHATIC COMPOUNDS

2.1 Derivatives of Methane. — Since the carbon atom is tetrahedral and the methane molecule symmetrical in space, as shown in the model (a), the four hydrogen atoms are equivalent, and if one of them

Methane (a) Monochloromethane (b) (c)



(a) (b) (c)

is imagined to be replaced by chlorine it is immaterial which one is selected. Replacement of the uppermost hydrogen of (a) gives (b); note that, in this model, made to scale, chlorine (radius 1.00 Å) is the largest atom, carbon (radius 0.77) is next, and hydrogen (radius 0.32) is the smallest. If the hydrogen shown in (a) to the right rear is replaced by chlorine, the result is (c), but this is the same as (b), only oriented in a different way. It is evident that only one monochloro derivative of methane is theoretically possible, and indeed only one substance of the formula CH_3Cl has been discovered; it is correctly defined as monochloromethane but is known by the simpler name methyl chloride.

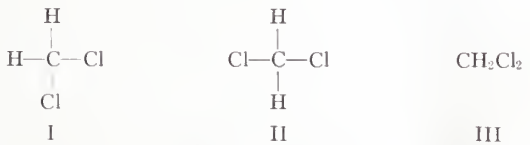
If any second hydrogen atom of either (b) or (c) is replaced by chlorine, the result is (d), which is the only possible spatial arrange- 2.2



(d)

Dichloromethane

ment for CH_2Cl_2, called methylene chloride. The model can be oriented in various positions, but there is no way in which switching of any pair of atoms gives rise to a different model. When a Kekulé formula is used, the corresponding model should be kept in mind. Thus formula I for methylene chloride appears different from II, but since they represent one and the same compound of space formula (d) they are understood to be equivalent representations. The flat



I II III

Methylene chloride

Equivalent formulas

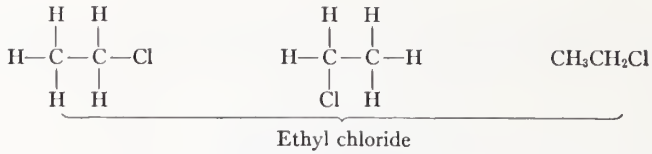
Kekulé formula shows merely which atoms are joined together, and not how the atoms are arranged in space. Formulas I and II indicate merely that the molecule is made up of a carbon atom to which two hydrogen and two chlorine atoms are attached. The formulas of trichloromethane (chloroform) and of tetrachloromethane (carbon tetrachloride) likewise represent one compound each:



Chloroform Carbon tetrachloride

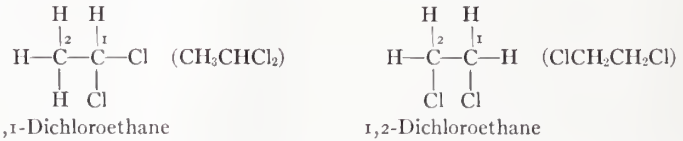
Derivatives of Ethane. — In ethane all six hydrogen atoms are identically situated and hence equivalent, and only one monosubstitution product is possible. The monochloro derivative, which can be described as monochloroethane but which is more generally known as ethyl chloride, is represented correctly by any one of the formulas shown, for each conveys the same information. 2.3

Monochloroethane



2.4 Isomerism becomes possible whenever two substituents are introduced into the ethane molecule, for these can either be located on the same carbon atom or distributed between the two carbon atoms. If two chlorine atoms are linked to one carbon atom, as in the formula below on the left, the compound represented can be distinguished from the isomer on the right by numbering the carbon atoms and

Numbering carbon atoms

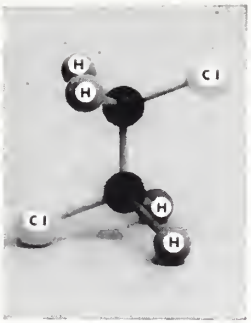


indicating the position of each chlorine atom by citing the number of the carbon atom to which it is joined. In the first compound both chlorines are attached to carbon atom No. 1 (or C_1), and hence the compound is 1,1-dichloroethane. The name 1-dichloroethane is incomplete and therefore incorrect; it would leave unspecified the location of one of the chlorine atoms. The name 1,1-chloroethane is incorrect because it implies 1-monochloroethane. The second dichloroethane is the 1,2-derivative. In this case the molecule is symmetrical and it makes no difference whether the carbon atoms are numbered from right to left, as shown, or in the reverse order. In the case of the isomer, left-to-right counting would give the alternate name, 2,2-dichloroethane, but a choice between the prefixes 1,1- and 2,2- is afforded by the rule that the numbers be kept as low as possible. However a formula is written, one should try all possible methods of counting the carbon atoms and select the name which gives the smallest numbers for the positions of the substituent groups.

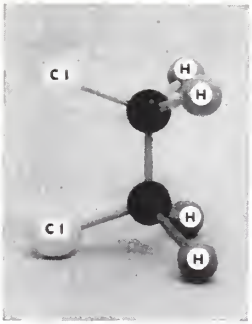
2.5 In the ball-and-stick model (a) for 1,2-dichloroethane the balls are not of accurate relative sizes, but the two large balls attached to carbon can be taken to represent chlorine atoms and the four smaller balls to stand for hydrogen atoms. If the lower carbon atom of the model is held stationary, the upper one can be rotated about the single bond connecting the two through an angle of 180°, and the result is (b). Models (a) and (b) represent two extremes, one (a) in which the chlorine atoms are maximally distant, and the other (b) in which the same atoms are as close as possible. Rotation to smaller angles theoretically could give an infinite number of other forms intermediate between (a) and (b). Experimentation shows that 1,2-dichloroethane

Freedom for rotation about a single bond

1,2-Dichloroethane



(a)



(b)

exists in only one form, and from this fact it is concluded that in the molecule itself the carbon atoms are as free to rotate about a single connecting bond, or pair of shared electrons, as are the balls in the models. The molecule is able, by rotation about the single bond, to assume the shape, or conformation, of greatest stability. It is known that even small hydrogens on adjacent carbon atoms exert a repulsive force if they come close to one another. Such mutual repulsions increase with increasing size of the atoms concerned. Since chlorine atoms are much larger than hydrogen atoms, the dominant factor in determination of the preferred conformation of 1,2-dichloroethane is the strong repulsion of chlorine-to-chlorine. Hence 1,2-dichloroethane exists predominantly in the conformation (a), in which the large chlorine atoms are as distant from each other as possible. Thus (a) is the form of maximal stability, and (b) is the form of minimal stability. The relationship is shown better in the Stuart models (a′)

Preferred conformation, a, a′



(a′)



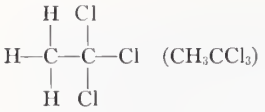
(b′)

1,2-Dichloroethane

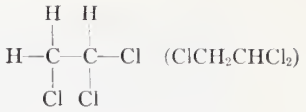
and (b′). Model (a′) has the greater symmetry, or balance, in that the large chlorine atoms are on opposite sides. In (b′) the two large halogen atoms are bunched on one side of the molecule, and the repulsion of one large chlorine for another chlorine in close proximity renders (b′) too unstable to exist.

Three chlorine atoms can be introduced into the ethane molecule in the following two ways:

Two isomers



1,1,1-Trichloroethane



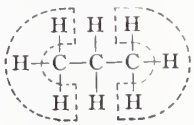
1,1,2-Trichloroethane

Note that with the second isomer the numbering of the carbon atoms from right to left, as the formula is written, gives smaller numbers (1,1,2-) than the alternate counting (1,2,2-). The two possible types of tetrasubstitution products are illustrated as follows:

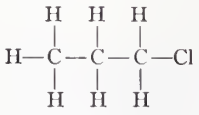
CH_2ClCCl_3 (1,1,1,2-) $\qquad$ $CHCl_2CHCl_2$ (1,1,2,2-)

Only one pentachloro and one hexachloro derivative are possible, for the situation is the same as with the penta- and hexahydrogen compounds.

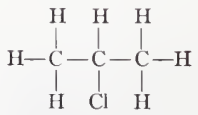
2.7 Derivatives of Propane. — The propane molecule presents a different situation because the eight hydrogen atoms are not all similarly located. The six hydrogens attached to the two terminal carbon atoms are equivalent (dotted lines), but the environment is different from that of the two hydrogens located on the central carbon atom. There is thus a differentiation between end and middle positions in the molecule; one result is that two isomeric monosubstitution products are possible, as exemplified by the monochloro derivatives:



Two isomers



($CH_3CH_2CH_2Cl$)
1-Chloropropane, or
n-propyl chloride



($CH_3CHClCH_3$)
2-Chloropropane, or
isopropyl chloride

These can be described as the 1-chloro and 2-chloro derivatives of propane but are more commonly called normal (*n*-) propyl chloride and isopropyl chloride. Although there is only one form of a methyl (CH_3—) or ethyl (C_2H_5—) group, the next higher hydrocarbon group can be the *n*-propyl group, $CH_3CH_2CH_2$—, or the isopropyl group, $(CH_3)_2CH$—. Polysubstitution in propane presents opportunity for isomerism of a still higher degree, and it is suggested that the student at this point derive the formulas and names of all possible dichloropropanes and trichloropropanes and compare his results with the answers given on the next page.

Dichloropropanes:		Trichloropropanes:	
$CH_3CH_2CHCl_2$	1,1-	$CH_3CH_2CCl_3$	1,1,1-
$CH_3CHClCH_2Cl$	1,2-	$CH_3CHClCHCl_2$	1,1,2-
$ClCH_2CH_2CH_2Cl$	1,3-	$ClCH_2CH_2CHCl_2$	1,1,3-
$CH_3C(Cl_2)CH_3$	2,2-	$CH_3CCl_2CH_2Cl$	1,2,2-
		$ClCH_2CHClCH_2Cl$	1,2,3-

Butanes. — The formula of ethane can be derived from that of methane by replacing one of the hydrogen atoms by a methyl group, and the propane formula can be built up similarly. This systematic method of derivation serves a useful purpose, for if all possible modes of substitution are considered, no isomers can be missed. Propane has two different types of hydrogen atoms, the type on the ends (a) and that in the middle (b), and hence in the derivation of the butanes substitution of each by methyl must be tried: 2.8

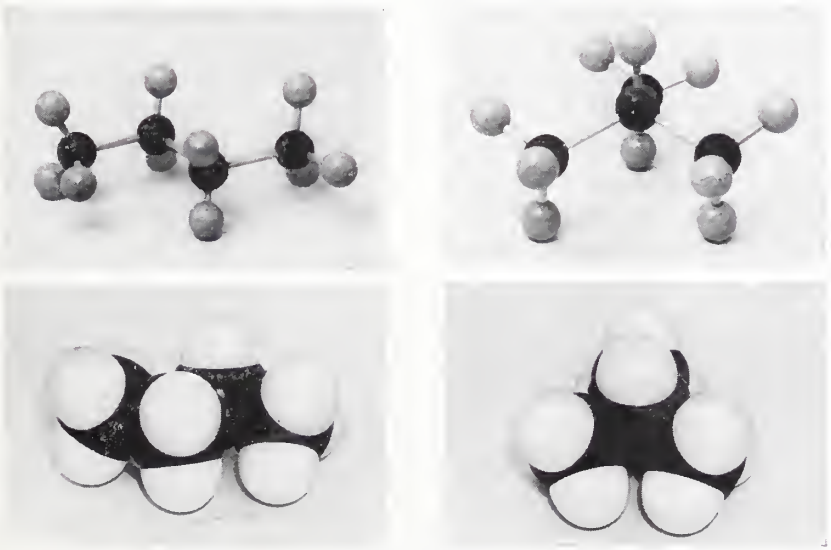
Methyl substitution in propane, $\overset{a}{CH_3}\overset{b}{CH_2}\overset{a}{CH_3}$, gives:

(a) $CH_3CH_2CH_2CH_3$
n-Butane
(b.p. $-0.5°$)

(b) CH_3CHCH_3 (with CH_3 branch)
Isobutane
(b.p. $-12°$)

2 BUTANES

Replacement of any one of the terminal hydrogens by a methyl group gives a straight-chain hydrocarbon of the formula C_4H_{10}, namely, normal butane. A similar operation on a centrally located hydrogen affords the isomeric, branched-chain hydrocarbon isobutane. The formula shown can be simplified by pooling the three methyl groups attached to the central carbon atom: $(CH_3)_3CH$. This formula sug-



n-Butane Isobutane

gests an alternate and descriptive name. The substance is seen to be a derivative of methane in which only one of the original hydrogens remains and the other three have been replaced by methyl groups; isobutane therefore can be named trimethylmethane, just as $CHCl_3$ is described as trichloromethane.

2.9 The spatial characteristics of *n*-butane and of isobutane are illustrated with photographs of two types of models (p. 23). Note the zig-zag arrangement of the methylene groups (CH_2) in *n*-butane, occasioned by the tetrahedral configuration of the carbon atoms. Isobutane, which has a branched-chain structure, has the lower boiling point, and is thus more volatile than the straight-chain isomer.

2.10 **Pentanes.** — Structural formulas of the C_5-hydrocarbons can be derived by the same systematic procedure of making all possible methyl substitutions in both butanes, and the only added operation necessary is to inspect the resulting formulas and eliminate duplicates:

From the butanes, $\overset{a\ b\ b\ a}{CH_3CH_2CH_2CH_3}$, $\overset{c\ d\ c}{CH_3CHCH_3}$ (CH_3 on c)

Three pentanes

are derived:

(a) $CH_3CH_2CH_2CH_2CH_3$

(b) $CH_3CH_2CHCH_3$ (CH_3)

[(c) $CH_3CHCH_2CH_3$ (CH_3) same as (b)]

(d) CH_3CCH_3 (CH_3)

It is seen that the third substitution tried (c) gives a formula identical with the second (b) and merely written in a different manner. Three distinct formulas remain and, since all possibilities have been investigated, the conclusion is reached that three pentanes can exist. The obvious name for the straight-chain hydrocarbon (a) is *n*-pentane. The branched hydrocarbon (b) can be regarded as a methyl-substitution product of the normal, or straight-chain, hydrocarbon having four carbon atoms in a row, that is, *n*-butane. Since the methyl group is linked to carbon atom no. 2 in the chain (right-to-left counting, since left-to-right counting would give a larger number), substance (b) is 2-methylbutane. The third isomer (d) could, on the same system (Geneva), be named 2,2-dimethylpropane, but a simpler name is evident from consideration that the substance has a central carbon atom with four attached methyl groups; it is $(CH_3)_4C$, or tetramethylmethane. The three pentanes are thus summarized as follows:

Names and boiling points of the three pentanes

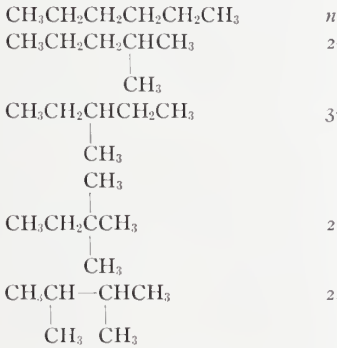
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	b.p. 36.1°
2-Methylbutane	$CH_3CH_2CHCH_3$ (CH_3)	b.p. 27.9°
Tetramethylmethane	$(CH_3)_4C$	b.p. 9.5°

Again, the most highly branched isomer has the greatest volatility.

Hexanes. — At this point the student should apply the systematic scheme of methyl substitution in all possible positions of the formulas of the three pentanes and thus determine the number of possible isomeric hexanes and their structures. According to the Geneva system, the basic name is that of the parent hydrocarbon corresponding to the longest chain of carbon atoms present: methane (C_1), ethane (C_2), propane (C_3), butane (C_4), pentane (C_5), hexane (C_6), etc. Methyl groups attached to the carbon chain are regarded as substituents, and their positions in the chain are indicated by numbers. Counting is done from whichever direction gives the smaller numbers. Try the problem before glancing at the answer, below. 2.11

Problem

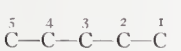
The correct solution of the problem is that five isomeric hexanes are possible. They are all known, and the structures and Geneva names are as follows: 2.12



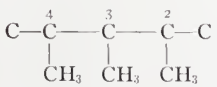
Five isomeric hexanes

Further Points about Names. — One method of study is to cover up the names, for example, of the hexanes written previously, and see if they can be reproduced from the formulas. Another is to cover up the formulas and see if they can be reproduced from the names. The way to do this can be illustrated with an example. To write the formula of 2,3,4-trimethylpentane, first write the carbon atoms of the basic hydrocarbon *n*-pentane: 2.13

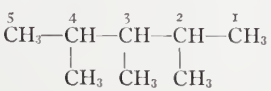
Formulas from names



Then attach the methyl groups in the proper positions:

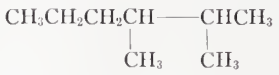


and then fill in hydrogen atoms until each carbon has the valence of four:



2.14 Note that the name 1,1,2-trimethylpentane for the hydrocarbon

Erroneous names



is at once seen to be incorrect, for attachment of a methyl group at C_1 of *n*-pentane makes it a hexane, not a pentane. The correct name is 2,3-dimethylhexane. "Heptamethylethane" is an obviously erroneous name, because ethane has only six positions for attachment of methyl groups.

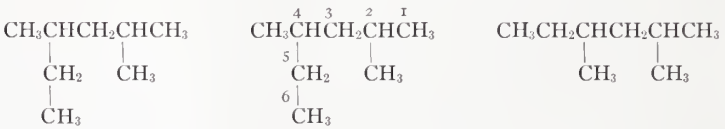
2.15 A formula often can be arranged in various ways, and sometimes the arrangement obscures the derivation of the Geneva name. Formula (1) is confusing because of the bracketing of the four methyl groups.



(1) (2) (3)

Actually one of the methyl groups at each end is part of the longest carbon chain, which is C_5, and the other is a substituent attached to this chain. The true situation is seen better in the arrangement (2) and most clearly when the formula is written as in (3); the hydrocarbon is 2,4-dimethylpentane. Another example, formula (4), is written in a way that tends to suggest that the substance is a methyl-

Count around the corner



(4) (5) (6)

ethyl derivative of pentane, since the carbon atoms written in a row form a chain of five. However, in selecting the longest chain one must consider all possible chains, including those that go around corners. The ethyl group at a right angle to the horizontal chain extends the chain to six, as shown by the numbers in (5). Had the formula been arranged as in (6), the correct name would have been obvious from the start: 2,4-dimethylhexane.

COMPOUNDS WITH FUNCTIONAL GROUPS

2.16 **Butyl Alcohols.** — In section 2.10 the formulas of the pentanes were derived by substitution of methyl for each of the four types of hydrogen atoms in the two butanes:



Substitution of methyl at (b) and at (c) gives the same hydrocarbon, and there are only three pentanes. If the group substituted for hydrogen in the butanes is anything other than methyl there are no duplicates and the number of isomeric derivatives is four. Thus systematic substitution of the hydroxyl group gives formulas for the four butyl alcohols:

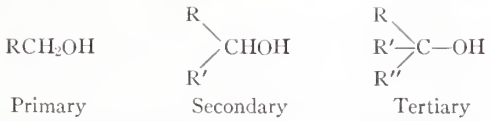
(a) $CH_3CH_2CH_2CH_2OH$

(b) $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$

(c) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH$

(d) $CH_3\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}\overset{\displaystyle OH}{\overset{|}{C}}H_3$

These isomers are usually known by common names assigned in part according to the alcohol types which they represent. An alcohol having just one alkyl group attached to the carbon carrying the hydroxyl is a primary alcohol. Secondary and tertiary alcohols have



Alcohol types

two and three alkyl groups, respectively, at the position indicated. Alcohols (a) and (c) are both primary; (a) has an *n*-propyl group linked to $—CH_2OH$, and in (c) the corresponding group is isopropyl. Isomer (a) is adequately described as *n*-butyl alcohol, and its isomer (c) is known as isobutyl alcohol. Alcohol (b), which has a methyl and an ethyl group linked to the hydroxylated carbon, is the only secondary alcohol of the series, and (d) is the only tertiary alcohol, and hence they are distinguished by prefixes which indicate the alcohol type: *sec-* (secondary) and *t-* (tertiary). The four alcohols are summarized as follows:

n-Butyl alcohol	$CH_3CH_2CH_2CH_2OH$
Isobutyl alcohol	$(CH_3)_2CHCH_2OH$
sec-Butyl alcohol	$CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$
t-Butyl alcohol	$CH_3-\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}-OH$

Formulas and common names

Geneva Names of Alcohols. — Alcohols of more complicated structure are usually known by their Geneva names. Just as hydrocarbons having a double or a triple bond are named alkenes (from

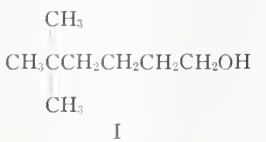
2.17

ethylene) or alkynes (from acetylene), alcohols are designated by changing the ending of the basic alkane from **-ane** to **-anol** (-ol from alcohol). Thus the Geneva name for methyl alcohol is methanol, and that for ethyl alcohol is ethanol. The hydroxyl group, or "ol" group, confers upon a molecule specific properties or functions; it is called a functional group, since it causes the compound to function in specific ways. Ethyl alcohol has the ability to react with sodium and with hydriodic acid (1.22) because it contains the alcohol functional group. Alkenes and alkynes similarly have specific reaction characteristics because of their functional groups: the double-bond, or ene group, and the triple-bond, or yne group.

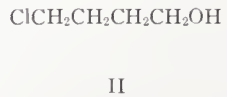
Functional groups

2.18 In order to apply Geneva names to the butyl alcohols, it is necessary first of all to select the **longest chain of carbon atoms that includes the maximum number of functional groups. The position of the functional group is then indicated by a number placed at the end of the name.** Isobutyl alcohol has one three-carbon chain which includes the two methyl groups, and another which includes one of these groups and the carbon carrying the hydroxyl group; the latter is selected and the compound is named 2-methylpropanol-1. *n*-Butyl alcohol is butanol-1, and *sec*-butyl alcohol is butanol-2. In case of a conflict, **functional group numbers take precedence over substituent group numbers.** Thus the basic name is decided upon first, that is, the substance is a butanol, a pentanol, etc., the carbon carrying the functional group is assigned the smallest possible number, and there is then no choice in numbers indicating the positions of substituent groups. Compound I is a dimethylhexanol, specifically 5,5-dimethyl-

Rules for naming



I



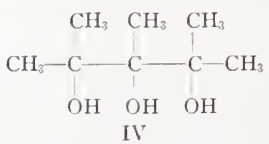
II

hexanol-1. Halogen, in the Geneva system, is treated as a substituent, and hence II is 5-chloropentanol-1 (not 1-chloropentanol-5). If two alcoholic hydroxyl groups are present, the substance is a diol; if three, it is a triol. Thus III is butanediol-1,4, and IV is 2,3,4-trimethyl-

Diols and triols

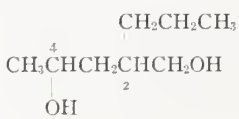


III



IV

pentanetriol-2,3,4. Compound V has one chain of seven carbon atoms,



V

but since this includes only one of the two alcoholic groups it is not selected as the basis for the name. Instead, the five-carbon chain including both groups is selected, for the basic name pentanediol shows that the compound is a diol and should function like other diols and not like monohydroxy alcohols. Attached to the pentanediol unit is a substituent group identified as an *n*-propyl group. Use of just the name propyl would be ambiguous, for it then would not be clear whether the group has the straight-chain structure of an *n*-propyl compound or is a branched-chain isopropyl derivative. The name of V is thus 2-*n*-propylpentanediol-1,4.

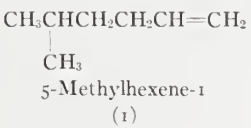
Alkenes. — The first two hydrocarbons of this series are usually referred to by their common names: ethylene, $CH_2{=}CH_2$; propylene, $CH_3CH{=}CH_2$. The Geneva system is used for higher alkenes, including the two butenes. In one of these the double-bond function is at the end of the chain and in the other it is at the middle. The terminal number indicating the position of the functional group gives

2.19

$CH_3CH_2CH{=}CH_2$ Butene-1 $\qquad$ $CH_3CH{=}CHCH_3$ Butene-2

Geneva names

the position of just the first of the doubly bonded carbons. The other principles of naming are as outlined in the preceding section. Examples (1) and (2) require no comment. Examples (3) and (4) show

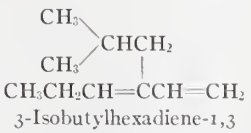


5-Methylhexene-1
(1)

$CH_3CH_2CH_2CH{=}CHCH_2CH_3$
Heptene-3 (not 4)
(2)

$CH_2{=}CHCH{=}CH_2$
Butadiene-1,3
(3)

$CH_2{=}CHCH{=}CHCH{=}CH_2$
Hexatriene-1,3,5
(4)



3-Isobutylhexadiene-1,3
(5)

that the system provides the convenient names diene and triene for compounds having two and three double bonds, respectively. Example (5) is a case where the basic name, hexadiene, is that including both functional groups, even though the six-carbon chain is not so long as that extending from the left-hand terminus and out along the branching group. Note that this four-carbon group is specifically the isobutyl group.

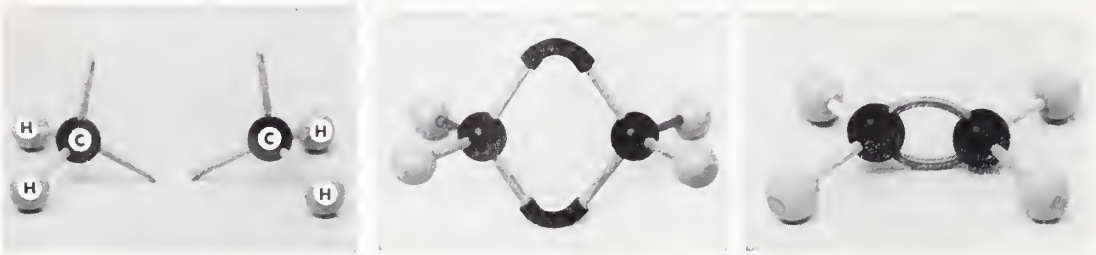
It should be noted that usage varies in application of the Geneva system of naming and that this term now refers to what is actually a

Geneva-I.U.C.-I.U.P.A.C. System

system modified by the International Union of Chemistry (1930) and the International Union of Pure and Applied Chemistry (1949). Thus "hexane" is used by some instead of "*n*-hexane"; some prefer "1-butanol" and "2-pentene" to "butanol-1" and "pentene-2"; "hexane-1,2,3-triol" rather commonly replaces "hexanetriol-1,2,3."

2.20 Space Models of Alkenes. — To make a ball-and-stick model of ethylene, some way has to be found for connecting the bonds of the two methylene groups (a). One way is to use sections of rubber tubing (b), and another is to replace the wooden sticks representing bonds by steel springs (c). The rubber connectors of (b) or the

Construction of model of ethylene



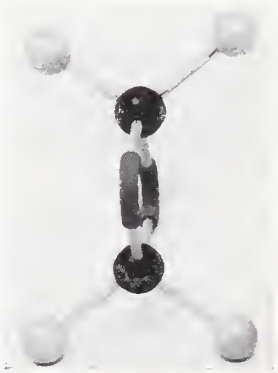
(a) (b) (c)

springs of (c) are of course under tension, which suggests that the double bond is under strain and hence prone to open to produce a strain-free ethane derivative. Hence the model leads to the expectation that ethylene and other alkenes are reactive compounds, which indeed is the case. Both alkenes and alkynes have potentialities for reaction not shared by alkanes. Since in alkanes all valences not involved in covalent C—C bonds are saturated with hydrogen, alkanes are described as saturated hydrocarbons. Alkenes and alkynes are unsaturated hydrocarbons.

Prediction of reactivity

Saturated and unsaturated hydrocarbons

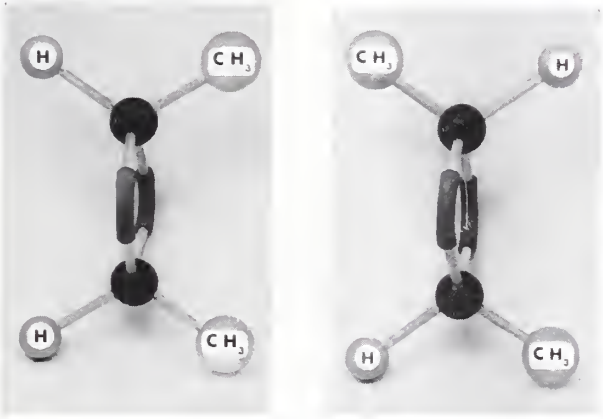
2.21 Geometrical Isomerism. — It will be noted from the model (c)



(d)

above, or from the same model arranged as in (d), that the four hydrogen and two carbon atoms of ethylene all lie in the same plane.

The molecule is symmetrical, or balanced, since the two hydrogens on the right-hand side are matched by two on the left-hand side. Inspection of the formula for butene-2, $CH_3CH{=}CHCH_3$, shows that here the situation is different. Each doubly bonded carbon has attached to it two atoms or groups which are different, methyl and hydrogen, and hence two arrangements in space are possible. In one arrangement (e) the two methyl groups are on the same side



(e) (f)

Two forms of butene-2

of the molecule, and in the other (f) they are across from each other, or on opposite sides; the double bond prevents conversion of one form to the other by rotation of one carbon atom. Butene-2 indeed exists in two isomeric forms, and these have the same structure, represented in the formula $CH_3CH{=}CHCH_3$, but differ in the orientation of their atoms in space, or in configuration. Any isomers which differ only in configuration, or spatial arrangement, are called stereoisomers, and the particular kind of stereoisomerism illustrated by the butenes is known as geometrical isomerism. Form (e) is called *cis*-butene-2, and form (f) is *trans*-butene-2. The prefixes come from the Latin prepositions *cis* and *trans*, meaning "on this side" and "across."

In models (e) and (f) the balls representing methyl are slightly larger than those representing hydrogen, although the difference is not fully in accordance with the difference in volume of the groups. The bonds connecting CH_3 to carbon should be longer than the carbon–hydrogen bonds, corresponding to the actual bond distances, which are: C—C, 1.54Å; and C—H, 1.09Å. Because of the difference in the size of the attached groups, model (f), with the two large groups on opposite sides of the molecule, has greater balance, or symmetry, than model (e), with the two bulky groups bunched on the same side. The actual shapes of the molecules are seen better in the Stuart models, which show more clearly the greater symmetry of the

2.22

trans-Form the more stable

trans-stereoisomer. *trans*-Butene-2 is significantly more stable than the *cis*-isomer. Under the influence of an appropriate catalyst, each

Stuart models



cis-Butene-2

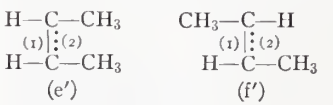


trans-Butene-2

compound can be isomerized in part to the other until equilibrium is reached, and the equilibrium mixture is found to be composed preponderantly of the *trans*-isomer and to contain only a minor amount of the *cis*-form. The relationship is the usual one: *trans*-isomers are almost invariably more stable than their *cis*-isomers. The greater stability is partly due to the greater symmetry, or better balance, of the *trans*-form, and partly to a repulsive effect. The Stuart models show that the two large methyl groups of *cis*-butene-2 are very close to each other, and hence repulsion of these groups must contribute to the instability of this isomer. The repulsive effect is analogous to that in the unstable form of 1,2-dichloroethane (2.5), but in the present case the double bond prevents rotation to a condition of greater stability.

2.23 For convenience in writing, models such as (e) and (f), page 31, are represented by the projection formulas (e′) and (f′). The methyl

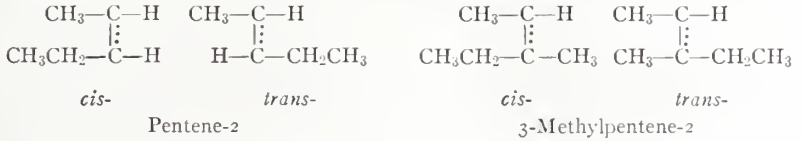
Projection formulas



groups and hydrogen atoms, which in the models are at an angle of 109° 28′, the normal tetrahedral angle, are written for simplicity on a line. One member of the double bond (1) is represented by a full line, to indicate that it extends above, or in front of, the plane of the paper or blackboard, and the other is represented by a dotted line, which is intended to indicate that this bond is below the plane of the paper, or to the rear. Inspection of models (e) and (f) will serve to identify these front and rear bonds, which lie in a plane at right angles to the plane of the six atoms.

2.24 Geometrical isomerism, or *cis-trans* isomerism, is possible when-

ever each of two doubly bound carbons carries two different atoms or groups, whether the groups attached to the first carbon are the same as those attached to the other or different. In pentene-2,

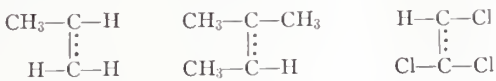


cis- *trans-* *cis-* *trans-*

Pentene-2 3-Methylpentene-2

Other examples

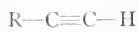
$CH_3CH_2CH{=}CHCH_3$, the two pairs of groups are different, in contrast to butene-2, but *cis-* and *trans-* forms are possible. It is not necessary that each doubly bonded carbon carry a hydrogen atom, and 3-methylpentene-2 is a typical case where one carbon carries two alkyl groups, but two that are different; the *cis*-isomer is identified as that in which hydrogen is *cis* to the smaller of the two groups. Geometrical isomerism is not possible if either carbon of an ene group carries two of the same atoms or groups, as in the examples listed:



No geometrical isomerism

Alkynes. — The model of acetylene (a) shows that the four atoms 2.25







No geometrical isomerism

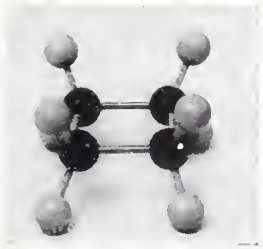
(a) (b) (c)

are in a line and hence that no opportunity exists for geometrical isomerism in alkynes describable as either monosubstituted acetylenes (b) or disubstituted acetylenes (c).

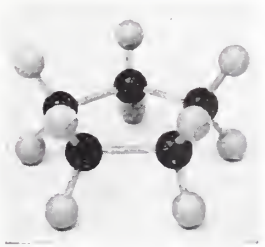
Cycloalkanes. — Examination of tetrahedral models with steel-spring bonds leads to the expectation that a hydrocarbon should be 2.26



Cyclopropane

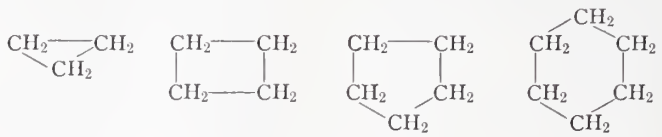


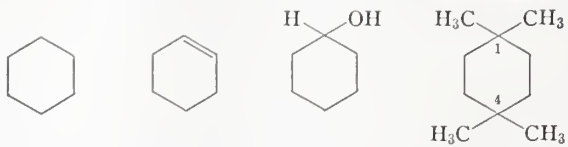
Cyclobutane



Cyclopentane

possible having three carbons joined in a ring and each saturated with hydrogen. The hydrocarbon is indeed known, and since it has the same number of carbon atoms as propane but is cyclic it is called cyclopropane. It is the first member of a series known as cycloalkanes. Cycloalkanes have the same type formula as alkenes, C_nH_{2n}. The formulas can be written in the manner shown, or abbreviated by writing just the connecting lines. Cyclohexane derivatives are particularly common and are conveniently represented with abbreviated formulas, as illustrated in the examples. The names cyclohexene and cyclohexanol require no number for indication of the position of the functional groups, since all six positions in cyclohexane are identical. The last example shows what is done when numbers (in this case substituent group numbers) are required.

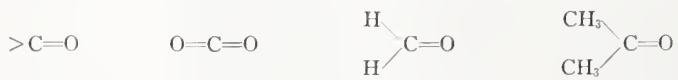




Cyclohexane Cyclohexene Cyclohexanol 1,1,4,4-Tetramethylcyclohexane

CARBONYL COMPOUNDS

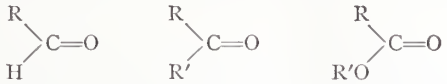
2.27 A carbon atom doubly bound to oxygen constitutes a carbonyl group, and simple compounds containing this group are illustrated in the formulas. The carbon–oxygen double bond is made up of two pairs of shared electrons, but, since oxygen is significantly more electronegative than carbon, carbonyl compounds have properties considerably different from carbon–carbon double-bonded compounds. Differences of only a quantitative nature distinguish the main types of carbonyl compounds, which are identifiable from the nature of the two groups attached to carbon. If one is an alkyl group and the other hydrogen, the compound is an aldehyde; formaldehyde is the only aldehyde having two hydrogens and no alkyl group. A



Carbonyl group | Carbon dioxide | Formaldehyde | Acetone

Types

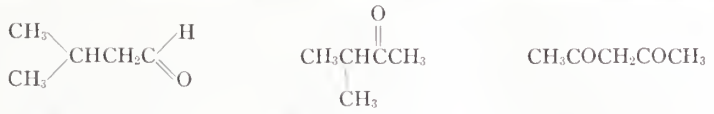
ketone contains two alkyl groups joined to the carbonyl carbon, and an ester contains one alkyl group and one alkoxyl group (RO—).



Aldehyde Ketone Ester

Geneva names

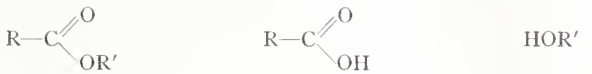
The carbonyl group is a functional group, and Geneva names are derived by adding to the basic name the suffix -al to indicate an aldehyde and -one to indicate a ketone as shown in the examples below. A number after the name indicates the position of the ketone or "one" group of a ketone; in an aldehyde the carbonyl group has to occupy a terminal C_1 position and hence a number is superfluous.



3-Methylbutanal 3-Methylbutanone-2 Pentanedione-2,4

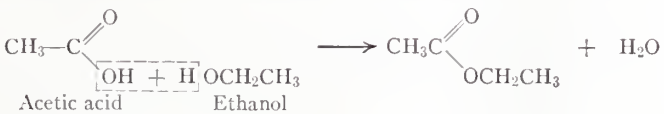
2.28

An ester is a derivative of an alcohol precursor, which furnishes the



Ester Carboxylic acid Alcohol

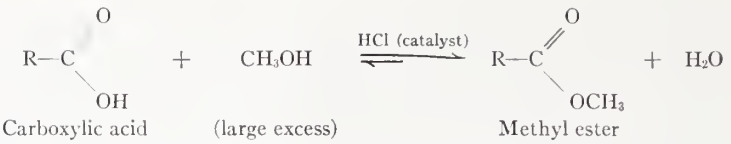
alkoxyl group, and of a carboxylic acid, so called because the group is a combination carbonyl-hydroxyl function. Ethyl acetate is the



Acetic acid Ethanol Ethyl acetate

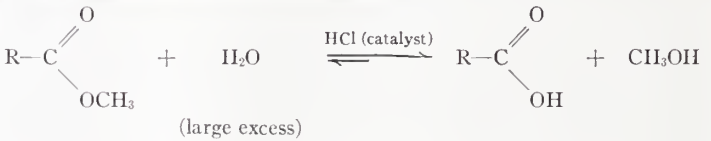
ethyl ester of acetic acid, derived by elimination of water between the molecules of the two components. If the formula is abbreviated to $CH_3COOC_2H_5$, one should remember that a double-bonded carbonyl group is present. Esters are generally made by heating the acid with a large excess of the alcohol and a trace of hydrogen chloride as catalyst. The reaction eventually reaches equilibrium; the catalyst greatly increases the speed with which equilibrium is reached but does not alter the position of equilibrium. A large excess of the alcoholic component, by the mass-action effect, shifts the equilibrium in favor of the ester and hence improves the efficiency of conversion of acid to ester. This procedure for formation of an ester was developed by E. Fischer and is known as the Fischer method of esterification.

Fischer esterification



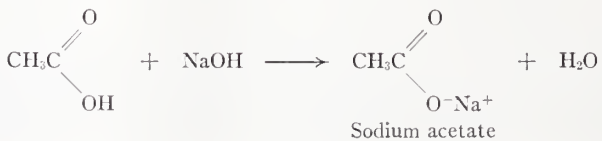
A catalyst accelerates the reverse reaction of an equilibrium just as it accelerates the forward reaction, and hence an ester is hydrolyzed to the components when heated with a large excess of water and a catalytic amount of hydrochloric acid:

Hydrolysis of an ester



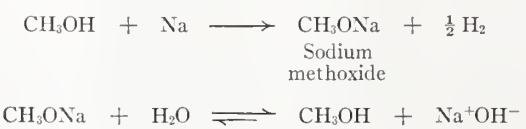
2.29 **Carboxylic Acids.** — Esters display at least some of the chemical properties characteristic of aldehydes and ketones, the typical carbonyl compounds, but carboxylic acids do not. The reason for this divergence is bound up with the acidic character of the carboxylic compounds. Acetic acid combines with sodium hydroxide in water solution to form a salt, sodium acetate, a polar compound containing sodium ions and acetate ions comparable to sodium chloride, Na^+Cl^-.

Ionic salt



These salts are stable to water and merely dissociate to the component ions. Sodium acetate is entirely different in behavior from sodium methoxide, the compound resulting from the action of sodium on methanol, for this is destroyed by water and converted into methanol and sodium hydroxide:

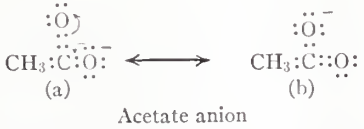
Contrast to RONa



Methanol contains a hydroxyl group, as does acetic acid, but this is not an acidic hydroxyl. Tested with indicator paper in water solution, methanol is neutral, whereas acetic acid shows a pH of about 3.

2.30 **Resonance.** — A simple and convincing explanation of why the one hydroxy compound is acidic whereas the other is neutral is afforded by the theory of resonance, a concept of very general application and usefulness introduced around 1930, largely by Linus Pauling at California Institute of Technology. According to the resonance theory,

when a substance can have two or more structures that are equivalent or nearly equivalent to one another and that are interconvertible by redistribution of valence electrons of either unsaturated or ionized centers, the actual molecule does not conform to any one of these structures but is a hybrid of them all, a resonance hybrid. Each resonance structure contributes to the character of the hybrid, and the greater the number of contributing structures the greater is the stability of the hybrid. Inspection of the electronic formula (a) for the acetate ion shows that the situation is favorable for electron redis-



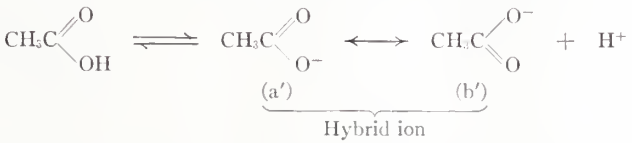
(a) (b)

Acetate anion

Redistribution of electrons

tribution. Carbon is joined to the upper oxygen by two pairs of shared electrons and to the oxygen at the right by one pair, and the latter oxygen carries the negative charge of the ion. If an electron pair originally shared with the upper oxygen moves entirely into the sphere of this oxygen (arrow) and a pair originally associated with the oxygen to the right moves into a shared position (arrow), the result is (b). The ionic charge is now on the upper oxygen because one of the two electrons that this atom has gained originally belonged to carbon and has been donated by carbon to oxygen, giving the oxygen a negative charge.

That the structures such as (a) and (b) are in resonance is indicated by a double-headed arrow; this means that the components are contributors to the hybrid that constitutes the actual entity, in this case an ion. The formation of a resonant hybrid acetate ion on dissociation of acetic acid can be represented with Kekulé formulas, as follows: 2.31



(a′) (b′)

Hybrid ion

Kekulé formulotion of resonance

The negative charge and the double bond can be located either as in (a′) or as in (b′), and these are identical resonance structures. The formulas meet the general requirement for resonance that electrons assume new orientations without any movement of atoms. It is important to avoid the misconception that the acetate ion has the structure (a′) one moment and (b′) the next and that the bonds are thrashing back and forth between the two positions. A mule does not alternate between being a horse and being an ass but is a hybrid having characteristics intermediate between those of a mare and a male ass.

2.32 As stated above, resonance is attended with stabilization. The acetate ion is stabilized by hybridization between two resonance structures and this stabilization provides a driving force promoting dissociation of acetic acid to a hybrid ion. Thus carboxylic acids owe their acidic character, or their ability to dissociate to give hydrogen ions, to the opportunity which the structure provides for formation of a resonance-stabilized hybrid carboxylate ion. Alcohols present no comparable opportunity for resonance stabilization of an ion and hence are not acidic.

Resonance stabilization of the ion

2.33 A further consequence of the resonance effect is that the carboxylate ion has no true carbonyl group. Each of the carbon–oxygen links is a double bond in one structure and a single bond in the other, and hence each is a hybrid bond of character intermediate between a double and a single bond. That carboxylic acids, unlike esters, do not enter into reactions characteristic of carbonyl compounds is thus understandable, since the usual reaction conditions are such that the acid is present in the form of its resonant ion.

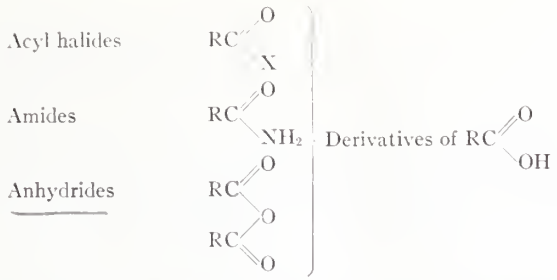
Lack of carbonyl properties

SUMMARY OF ALIPHATIC TYPES

2.34 The preceding pages have included at least some reference to the structures and names of nearly all the important classes of aliphatic compounds. These fall into groups, as summarized below.

	HYDROCARBONS	
Alkanes	RH	C_nH_{2n+2}
Alkenes	$>C=C<$	C_nH_{2n}
Alkynes	$-C\equiv C-$	C_nH_{2n-2}
Cycloalkanes	$(CH_2)_n$	C_nH_{2n}
	ALCOHOLS AND DERIVATIVES	
Alcohols	ROH	$C_nH_{2n+1}OH$
(primary, RCH_2OH; secondary, $RR'CHOH$; tertiary, $RR'R''COH$)		
Alkyl halides	RX	$C_nH_{2n+1}X$
Methyl ethers	$ROCH_3$	$C_nH_{2n+1}OCH_3$
Amines	RNH_2	$C_nH_{2n+1}NH_2$
	CARBONYL COMPOUNDS	
Aldehydes	RCH=O	$C_nH_{2n+1}CHO$
Ketones	RR'C=O	$C_nH_{2n+1}COC_nH_{2n+1}$
Methyl esters	$RC(=O)OCH_3$	$C_nH_{2n+1}C(=O)OCH_3$
	HYBRID-CARBONYL COMPOUNDS	
Carboxylic acids	$RC(=O)OH$	$C_nH_{2n+1}C(=O)OH$

2.35 Only a few additions are needed to complete the list of aliphatic types. Formally analogous to the derivatives of alcohols, RX, RNH_2, and ROR, are the following derivatives of acids:



Physical Properties. — At ordinary temperature, methane, ethane, propane, and *n*-butane are gases, the normal (straight-chain) alkanes from C_5 through C_{17} are liquids, and those of carbon content C_{18} and higher are solids. The hydrocarbon *n*-heptacontane of the formula $C_{70}H_{142}$ has been synthesized and found to have the melting point 105° and to be distillable in high vacuum (pressure of 0.00001 mm. of mercury). The transition from gas to liquid to solid with increasing molecular weight is analogous to that noted in the series of halogens: Cl_2, a gas; Br_2, a liquid; I_2, a solid. In Fig. 2.36 the boiling points

2.36

Physical state

Boiling points

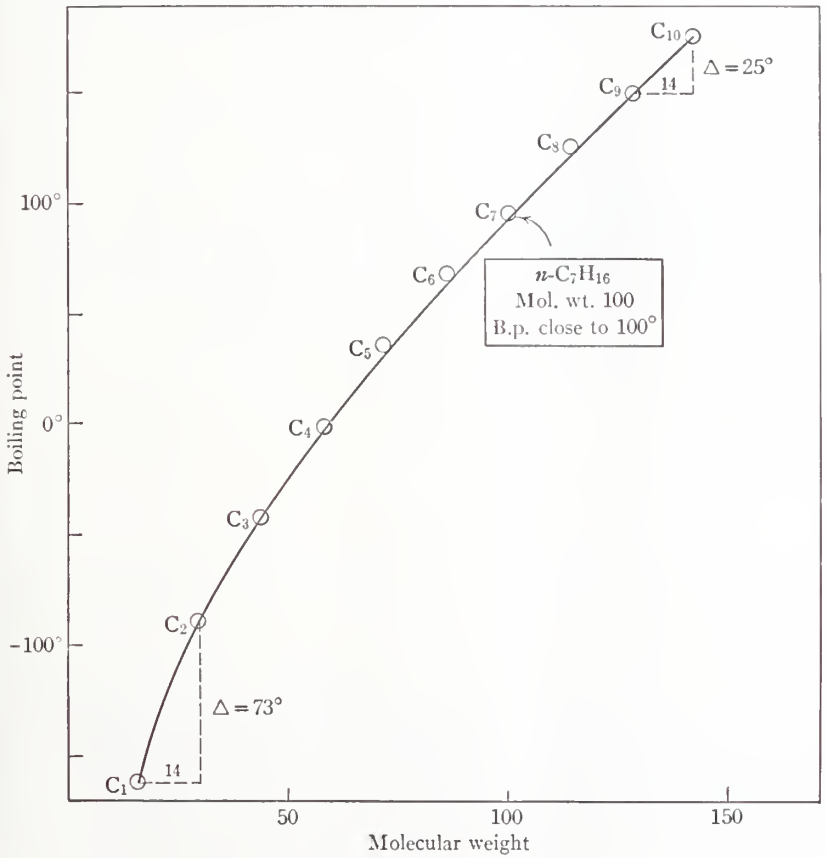


FIG. 2.36. — Boiling Points of *n*-Alkanes

of the first ten *n*-alkanes are plotted against their molecular weights. The curve rises steeply at first, for the increase of molecular weight of 14 units for each CH_2 represents a large proportional change when the molecular weight is small. Thus the C_1 and C_2 homologs differ in boiling points by 73°, but the C_9 and C_{10} homologs differ by only 25°. The relationship means that lower alkanes are more easily separable by fractional distillation than higher alkanes. The chart also brings out a point of reference useful to remember: the *n*-alkane of molecular weight 100 has a boiling point close to 100°. The chart for *n*-alkanes typifies the relationship generally found for other compounds which, in the liquid phase, are unassociated and not bound together in aggregates. If a straight-chain aliphatic compound is known to belong to one of the unassociated types, the boiling point can be inferred with at least a fair degree of approximation from Fig. 2.36. In the case of a branched-chain compound, allowance can be made for the fact that branching produces some increase in volatility (2.9).

Unassociated liquids

2.37 The degree of accuracy of the generalization that unassociated liquids of molecular weight of about 100 boil at about 100° can be seen from Table 2.37. Both saturated and unsaturated hydrocarbons

TABLE 2.37

Correlation of Molecular Weight and Boiling Point

Compound	*Mol. Wt.*	*B.P.*	*Type*
$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	100.20	98.4°	Alkane
$CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$	98.18	93.1°	Alkene
$CH_3CH_2CH_2CH_2CH_2C{\equiv}CH$	96.17	99.6°	Alkyne
$CH_3CH_2CH_2OCH_2CH_2CH_3$	102.17	90.5°	Ether
$CH_3CH_2CH_2CH_2CH_2Cl$	106.60	105.7°	Alkyl halide
$CH_3C(=O)OCH_2CH_2CH_3$	102.13	101.7°	Ester
$CH_3CH_2CH_2C(=O)Cl$	106.55	102°	Acid chloride
$CH_3CH_2CH_2N(H)CH_2CH_2CH_3$	101.19	110.7°	Amine
$CH_3CH_2CH_2CH_2C(=O)H$	101.16	129°	Aldehyde
$CH_3CH_2C(=O)CH_2CH_2CH_3$	100.16	124°	Ketone

conform reasonably well to the rule, as do ethers, alkyl halides, esters, and acid chlorides. Amines, aldehydes, and ketones deviate to a slight degree and hence appear to be slightly associated.

2.38 Alcohols and carboxylic acids deviate markedly from the rule, as shown by the following data:

$CH_3CH_2CH_2CH_2CH_2CH_2OH$ Mol. Wt. 102.17 B.P. 156°

$CH_3CH_2CH_2CH_2C(=O)OH$ Mol. Wt. 102.13 B.P. 187°

Associated liquids

The high boiling points indicate that in the liquid state both compounds are associated into aggregates of molecules of aggregate weight higher than the molecular weight of the monomer, or single molecule. Both compounds contain a hydroxyl group, as does water, and water, of molecular weight only 18.02 but the high boiling point of 100°, is clearly associated in the liquid state. Water evidently is associated to an even greater degree than the alcohols, since $CH_3CH_2CH_2OH$ has a boiling point (97°) close to that of water but is of considerably higher molecular weight (60.09). The association of liquid alcohol molecules, like the association of water molecules, is attributed to the phenomenon of hydrogen bonding. The hydroxylic hydrogen atom of one monomer is attracted by the strongly electronegative oxygen

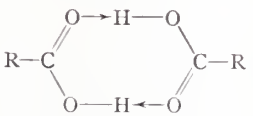
Hydrogen bonding



Alcohol monomer (vapor) Alcohol dimer (liquid)

of a second molecule with the result that the hydrogen forms a bridge, or hydrogen bond, linking the two oxygen atoms. The bonding of oxygen to hydrogen through an unshared pair of electrons is represented by an arrow pointing to hydrogen. The high boiling point of the alcohol is attributable to the fact that heat energy is required to break the hydrogen bond and liberate monomeric vapor.

Carboxylic acids boil at temperatures even higher than alcohols of the same molecular weight, as evident from the comparison cited above. This property is attributed to the fact that the structure permits two-fold hydrogen bonding in the dimer: 2.39



Carboxylic acid dimer

Evidence of physical chemistry shows that liquid carboxylic acids do indeed exist largely in dimeric form. Formic acid, HCOOH, has a boiling point of 100.5°, which is about that of unassociated liquids of molecular weight comparable to that of formic acid dimer: $(HCOOH)_2 = 92$.

Solubility Relationships. — An important principle of solubility can be expressed in the simple statement that like dissolves like. A hydrocarbon liquid is likely to be found a good solvent for solids that are also hydrocarbons, preferably of the same hydrocarbon type. 2.40

Liquid alkanes (e.g., *n*-hexane) dissolve paraffin wax from petroleum, for this is a mixture of saturated hydrocarbons of the alkane type. Methanol is a poor solvent for paraffin because it is unlike it chemically, since it contains a hydroxyl group. Water contains a hydroxyl group, and the two like, hydroxylic compounds, methanol and water, are miscible with each other in all proportions. Ethyl and *n*-propyl alcohol are also sufficiently hydroxylic in overall character to be infinitely soluble in water. Beyond the C_3 alcohol, the hydrocarbon part begins to be the dominating characteristic of the molecule and solubility in water steadily decreases. Thus *n*-hexyl alcohol, $CH_3CH_2CH_2CH_2CH_2CH_2OH$, is more like an alkane than it is like water and the solubility in water is only 1 g. per 100 g. of water. Conversely, the solubility of alcohols in hydrocarbon solvents increases with increasing size of the alkyl group. As compared with an ordinary alcohol of the same molecular size, a compound with two alcoholic hydroxyl groups shows increased solubility in water and decreased solubility in a solvent such as *n*-hexane. Carboxylic acids are also hydroxylic and they exhibit solubility relationships comparable to those of alcohols. On the other hand, esters, ethers, and alkyl halides resemble hydrocarbons in the nature of the substances with which they mix or in which they are capable of being dissolved.

SUMMARY

Alkanes

Methane. Tetrahedral nature of carbon means that all four hydrogens of methane are equivalent; hence there is only one CH_3Cl (methyl chloride), one CH_2Cl_2 (methylene chloride), one $CHCl_3$ (chloroform), one CCl_4 (carbon tetrachloride).

Ethane. All six hydrogens are equivalent and hence only one monochloro derivative is possible. Two dichloro derivatives: 1,1-dichloroethane (both chlorines on the same carbon) and 1,2-dichloroethane (one chlorine on each of the two carbons). In 1,2-dichloroethane the carbon atoms are free to rotate about the single connecting bond. Repulsive forces between atoms increase with increasing proximity and with increasing size of the atoms (or groups). Hence the most stable form, or conformation, of 1,2-dichloroethane is that in which the two large chlorine atoms are on opposite sides, or maximally separated; the least stable conformation is that in which the two large chlorine atoms are bunched on one side of the molecule. Trichloroethanes: 1,1,1-; 1,1,2-. Tetrachloroethanes: 1,1,1,2-; 1,1,2,2-. One pentachloro and one hexachloro derivative.

Propane. Two types of positions for substitution: central and terminal. *n*-Propyl chloride and isopropyl chloride. Four dichloropropanes; five trichloropropanes.

n-Butane and isobutane (branched isomer the more volatile). Derivation of the formulas from formula of propane by substitution of methyl for hydrogen atoms of the two types present. Abbreviation: isobutane = $(CH_3)_3CH$ = trimethylmethane.

Pentanes (3 isomers). Derivation of formulas by systematic methyl-substitution in the two butanes. Isomers: $CH_3(CH_2)_3CH_3$, *n*-pentane; $CH_3CH_2CH(CH_3)_2$, 2-methylbutane (Geneva name); $(CH_3)_4C$, tetramethylmethane (the most volatile).

Hexanes (5 isomers). Derivation as above. Geneva nomenclature: name as derivative of the parent hydrocarbon having the longest carbon chain; positions of substituents indicated by numbers; counting done in direction giving the smallest numbers.

About names. Practice both naming compounds and writing formulas from names. Watch for an erroneous name or formula (check the C valences). Consider all possible chains, including those going around a corner.

Butyl alcohols (4 isomers). Derivation by OH-substitution in the two butanes. Alcohol types: primary, RCH_2OH; secondary, R_2CHOH; tertiary, R_3COH. The isomeric alcohols: *n*-butyl (primary), isobutyl, $(CH_3)_2CHCH_2OH$ (primary); *sec*-butyl, $CH_3CH_2CH(OH)CH_3$; *t*-butyl, $(CH_3)_3COH$.

Geneva names of alcohols: methanol, ethanol. Functional groups: OH (ol), >C=C< (ene), —C≡C— (yne). Select longest C-chain that includes maximum number of functional groups. Functional group number takes precedence over substituent group number. Diols and triols.

Alkenes. Common names used for ethylene, propylene, isobutene. Geneva names for higher enes, dienes, trienes.

Geometrical isomerism. Space models of ethylene; connections by rubber tubes or by springs. Butene-2, $CH_3CH=CHCH_3$, exists in *cis*- and *trans*- forms. Stereoisomers. Models show that *trans*-isomer, with large methyl groups on opposite sides, has greater balance, or symmetry, than *cis*. *trans*-Isomer more stable than *cis* because of greater symmetry and also because in *cis*-isomer repulsion of large groups close to each other contributes to instability. Planar projection formulas (full line for bond extending to front, dotted line for rear bond). Other examples of geometrical isomerism: $CH_3CH=CHCH_2CH_3$, $CH_3CH=C(CH_3)CH_2CH_3$.

Alkynes. All four atoms of H—C≡C—H in a line. Geometrical isomerism not possible.

Cycloalkanes. Formulas and models of cyclopropane, cyclobutane, cyclopentane, cyclohexane. Abbreviated formulas for cyclohexene, cyclohexanol, 1,1,4,4-tetramethylcyclohexane.

Carbonyl Compounds

Carbonyl group of CO_2, O=C=O; formaldehyde, $CH_2=O$; acetone, $(CH_3)_2C=O$. Type formulas of an aldehyde, RHC=O; a ketone, $R_2C=O$; an ester R'O(R)C=O. Geneva: -al, for aldehyde, -one for ketone, e.g., 3-methylpentanal, 3-methylbutanone-3, pentanedione-2,4.

An ester is derived from a carboxylic acid component and an alcohol component. CH_3COOH (acetic acid) + $HOCH_2CH_3$ (ethyl alcohol) − H_2O ⟶ $CH_3COOCH_2CH_3$ (ethyl acetate). E. Fischer method of esterification: an acid + excess methanol + HCl (catalyst) ⇌ the methyl ester (equilibrium displaced by excess methanol). Hydrolysis by excess water + HCl as catalyst.

Carboxylic acids. Acetic acid dissociates to H^+, is a weak acid: $CH_3COOH \rightleftharpoons CH_3COO^- + H^+$. Forms sodium acetate, $CH_3COO^-Na^+$.

Resonance theory (Pauling, 1930): when a substance can have two or more equivalent structures interconvertible by electron redistribution, it is a resonance hybrid of all of them. Resonance stabilizes the molecule; the larger the number of contributors, the greater is the stability. Electronic formulas of two resonance structures of the acetate ion: electrons move out of the sphere of one oxygen and into the sphere of the other, and negative charge changes place. Kekulé formulation of hybrid acetate ion. Resonance stabilization of the acetate ion provides driving force for its formation. Consequence of resonance: a carboxylic acid has no true carbonyl group and, unlike an ester, does not give carbonyl reactions.

Summary of Aliphatic Types

See tabular summary, 2.34, 2.35. Physical properties. Boiling points increase with increasing molecular weight. An unassociated liquid of molecular weight 100 has a b.p. close to 100°. Alcohols are higher boiling because of hydrogen bonding: ROH←OR. Carboxylic acids have even higher boiling points because of two-fold hydrogen bonding in dimeric aggregate.

Solubility relationships. Like dissolves like. Hydrocarbon solids dissolve in hydrocarbon solvents, not in water or methanol. Methanol, ethanol (hydroxylic) are miscible with water (HOH), *n*-hexyl alcohol is nearly insoluble in water but soluble in hydrocarbon solvents.

PROBLEMS

1. Formulate and name all possible dibromo derivatives of isobutane (3 isomers) and of *n*-butane (6 isomers).
2. Write formulas for all heptanes derived from $CH_3CH(CH_3)CH_2CH_2CH_3$ and give the Geneva names.
3. Write structural formulas for:
   (*a*) 1-Bromo-2-chlorononane
   (*b*) 2,2,3-Trichloroheptane
   (*c*) 2-Bromo-2-methylbutane
   (*d*) Tetraethylmethane
4. Give Geneva names for:
   (*a*) $CH_3CH(CH_3)CH_2CH_2CH(CH_3)CH_2CH_3$
   (*b*) Isobutane
   (*c*) $CH_3CH_2CH_2CH(C_2H_5)CH_3$
   (*d*) $(CH_3)_2CHCH(C_2H_5)CH_2CH(CH_3)_2$
5. What octanes can be derived from the heptane $CH_3CH_2CH_2C(CH_3)_3$? Give the Geneva names.
6. Give the Geneva names for:
   (*a*) CH_2CHCH_2 (Glycerol)
   OH OHOH
   (*b*) $(CH_3)_2CCH_2CHCH_2CH_3$
   OH CH_3
   (*c*) $CH_3CH_2CHCH{=}CHCH(CH_3)_2$
   CH_3
   (*d*) $CH{\equiv}CCH_2CHCH_3$
   CH_2CH_3
   (*e*) $(CH_3)_2C{=}CHCH{=}C(CH_3)_2$
   (*f*) $(CH_3)_2CHCHCH(CH_3)CH_2OH$
   $CH_2CH{=}CH_2$
   (*g*) $CH_3CHCH_2CHCH_2CH_3$
   $CH_3CHCH_2CH_2$
   (*h*) $CH_2CH_2C{=}O$
   $CH_2CH_2C{=}O$
7. Write formulas for:
   (*a*) 2-Methyl-3-ethylpentanol-1
   (*b*) 1,4-Diphenylbutadiene-1,3
   (*c*) Trimethylethylene
   (*d*) Butanediol-2,3
   (*e*) 5-Chloro-4-methylpentene-1
8. Give the Geneva names of all alcohols that are monohydroxy derivatives of
   $CH_3CH_2CH_2CHCH_3$.
   CH_2CH_3
9. Propionic acid has the formula $C_3H_6O_2$. Write formulas showing the structures of the following derivatives:
   (*a*) Methyl propionate
   (*b*) Isopropyl propionate
   (*c*) Propionyl chloride
   (*d*) Propionic acid anhydride
10. Ethanol has a hydroxyl group, like acetic acid; why is it neutral and not acidic?
11. In the carbonate ion, $CO_3^{=}$, the three oxygens are symmetrically spaced and equidistant. Write all possible resonance structures.
12. From the formulas of the three pentanes, derive the formulas for all possible monohydroxy derivatives (8 isomers). These are called amyl alcohols ($C_5H_{11}OH$).

CHAPTER 3

REACTIONS OF ALIPHATIC HYDROCARBONS

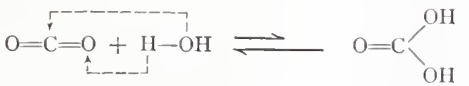
3.1

The reactions to be discussed are of two types, substitution and addition. An illustrative substitution reaction already mentioned is the reaction of ethyl alcohol with hydriodic acid to form ethyl iodide and water; the hydroxyl group of the molecule is substituted by

$$CH_3CH_2OH + HI \longrightarrow CH_3CH_2I + H_2O$$

Substitution reaction

iodine. Reactions of this type are also described as displacements. A familiar addition reaction is that which occurs when carbon dioxide is dissolved in water. The double bond of one of the carbonyl groups opens, and the hydrogen of a water molecule joins to oxygen and the



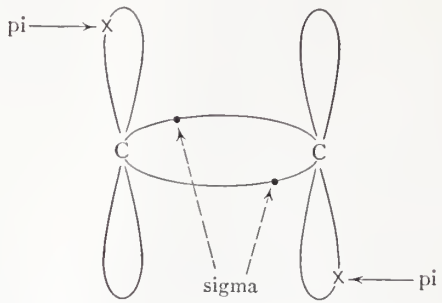
Carbonic acid

Addition reaction

hydroxyl group joins to carbon. Only a small amount of carbonic acid is formed, for the reaction is reversible and the reverse reaction, elimination of water, predominates over addition. Some addition reactions are reversible; some are irreversible. Additions to unsaturated compounds are possible because of the presence of electrons in excess of the one pair required for bonding the unsaturated atoms. Actually the two electron pairs that comprise a double bond have different properties because the electrons travel in orbitals of different types. The electrons of one pair are called sigma electrons, and those of the other pair are pi electrons. The nature of the two types of orbitals is indicated roughly in the diagram; the pi electrons are in loop-like orbitals with a plane of vibration perpendicular to the plane

Sigma and pi electrons

of the sigma bond. The protruding pi electrons are thus available for formation of more stable sigma bonds with other atoms.



3.2 **Alkanes.** — The alkanes are fully saturated and have no pi electrons available for addition reactions. Reactions of substitution are the only type possible, and although reactions of this type do exist they are not numerous. Methane, ethane, propane, and the higher normal (straight-chain) hydrocarbons are inert to a number of reagents. If *n*-hexane, a liquid, is shaken with concentrated sulfuric acid, it neither dissolves nor reacts, and the hydrocarbon (sp. gr. 0.66) subsequently separates as an upper layer in unchanged form. *n*-Hexane is not attacked by molten alkali, or by hot nitric acid, or by potassium permanganate, or other strong oxidizing agents. *n*-Hexane does react with chlorine and with bromine, but only under special conditions. If a test tube containing *n*-hexane is put in a dark place, treated with a drop of bromine, stoppered, and let stand at room temperature in the absence of light, the initial color of bromine remains in undiminished intensity for days. If the solution is exposed to sunlight, the color fades completely in a few minutes and hydrogen bromide is detected as one reaction product by breathing across the mouth of the test tube, when the acid condenses on moisture of the breath to form a cloud. The reaction is a substitution:

Inert character

Photochemical halogenation

$$C_6H_{14} + Br_2 \xrightarrow{\text{Light}} C_6H_{13}Br + HBr$$

It is more fully described as a light-induced, or photochemical, bromination. Alkanes are generally capable of being brominated or chlorinated photocatalytically, but they are inert to the less reactive iodine.

3.3 It is sometimes possible to deduce the mechanism of a given reaction, that is the sequence of steps leading from reactants to products, and so to understand better why the reaction proceeds. A clue to the mechanism may be gained from an investigation of the rate of the reaction as the concentration of each reactant is varied, or with change in temperature or solvent. In the case under discussion an important

clue is that radiant energy is required. Light is known to have the power to split the chlorine molecule into two chlorine atoms. This splitting is an example of a general phenomenon known as homolysis, in which a covalent bond is severed and one electron is retained by each of the atoms forming the bond: $A:B \longrightarrow A\cdot + B\cdot$. The fragments produced on homolytic fission are called free radicals, and each carries an odd, or unpaired, electron. Free radicals are highly reactive, because of the tendency of atoms to attain their normal-valence shell. When the chlorine molecule, written below (1) with just the bonding electrons, suffers light-induced homolysis, the two fragments produced are best described as chlorine free radicals. Such a radical has

Free-radical reaction

$$\begin{array}{lrcl} 1. & Cl{:}Cl & \xrightarrow{\text{Light energy}} & Cl\cdot + Cl\cdot \\ 2. & Cl\cdot + RH & \longrightarrow & HCl + R\cdot \\ 3. & R\cdot + Cl_2 & \longrightarrow & RCl + Cl\cdot \end{array}$$

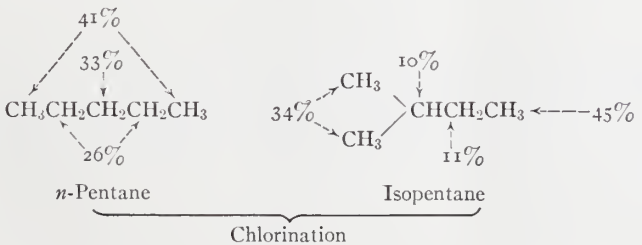
Reaction mechanism

only transient existence. Because of its high reactivity it is able to attack a molecule of the alkane as in (2) to form hydrogen chloride and an alkyl radical, which in turn attacks a chlorine molecule (3) with production of the chloroalkane. Chlorine radicals, which participate in the initiating reaction (2), are regenerated in reaction (3), and the two reactions together constitute a chain which, if both reactions proceeded with perfect efficiency, would be self-propagating without further requirement of light energy. The efficiency, however, is not perfect, for chlorine radicals can combine to reform Cl_2, or dissipate energy by collision with the flask walls. Hence continued irradiation is necessary to maintain an adequate supply of initiating radicals.

Photochemical halogenation is one of several examples of reactions believed to proceed by free-radical mechanisms. It is generally characteristic of such reactions that they can be induced in one or all of three ways: by light, by heating to a high temperature, which favors radical formation, and by the catalytic action of a peroxide capable of ready decomposition to radicals: $RO{:}OR \longrightarrow 2\ RO\cdot$. Alkanes can be chlorinated by all three methods. Another characteristic of free-radical reactions is that the attack is at random positions. In the thermal chlorination of *n*-pentane and isopentane all possible

3.4

Character of free-radical reactions



Random attack

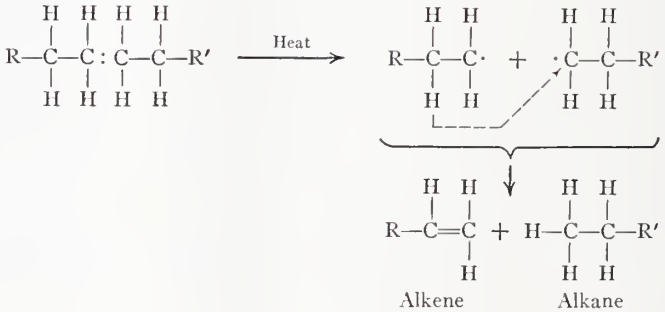
positions are substituted, as can be seen from the charts giving the relative proportions of the different isomers. The data are derived from study of a commercial process in which a petroleum fraction containing *n*-pentane and isopentane is chlorinated in the dark at a temperature (200°) sufficient to produce initiating radicals. The mixture of chloropentanes is useful both as a solvent and for conversion to a mixture of alcohols that goes into the making of quick-drying automobile lacquers.

3.5

Cracking of alkanes

The cracking, or thermal decomposition, of alkanes is a reaction of great importance in the production of motor fuels and will be discussed more fully in a later chapter. The process involves passing vapor of an alkane mixture through a hot tube (500°) to effect rupture of carbon–carbon linkages and cleavage of large molecules into smaller fragments. The type of reaction involved is shown in the formulation. Homolysis of the covalent bond, or electron pair, produces two free radicals, and these become stabilized by transfer of hydrogen from

Homolysis to radicals



one to the other, to form an alkene from one radical and an alkane from the other. The burning of gasoline in an internal combustion engine is a high-temperature reaction which undoubtedly involves initial cracking of hydrocarbons to free radicals. The radicals pro-

Molecular oxygen

duced combine readily with oxygen, since oxygen itself is a diradical (odd electron on each atom).

ALKENE ADDITIONS

3.6

The double bond of an alkene makes the molecule far more reactive than an alkane and capable of undergoing addition reactions, rather than substitutions, because the pi electrons (×) are capable of binding other atoms. Thus gaseous ethylene adds chlorine at room temperature without catalysis by light or by a peroxide to form liquid ethylene dichloride in good yield. The conversion of

$$CH_2{=}CH_2 + Cl_2 \longrightarrow ClCH_2{-}CH_2Cl$$



Ethylene dichloride

gaseous hydrocarbons into liquid dihalides led early chemists to describe them as olefins (oil-forming substances), and the terms olefin, olefinic hydrocarbon, olefinic linkage are still used. The addition is an example of a very general reaction, for nearly all alkenes are capable of adding chlorine, bromine, and even iodine, the least reactive halogen. Since halogen addition is not dependent upon conditions favoring formation of free radicals, it evidently does not proceed by a free-radical mechanism. One clue to the mechanism is that the reaction is catalyzed by a mineral acid. For example, addition of bromine to hexene-1 is speeded up by a trace of hydrobromic acid. Since the catalyst is an ionic compound, H^+Br^-, the observation suggests that one or more transient ionic intermediates are involved, and hence that the addition proceeds by an ionic mechanism. The idea is strengthened by the fact that, under suitable conditions and in the absence of bromine, H^+Br^- itself adds to alkenes, for example, to butene-2.

Addition of halogen

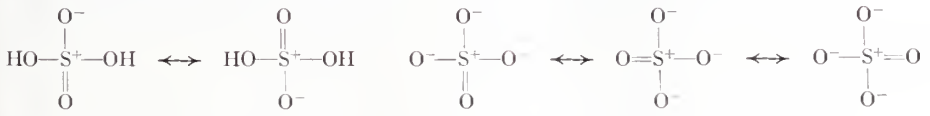
Catalyzed by H^+Br^-

$$CH_3CH{=}CHCH_3 + H^+Br^- \longrightarrow CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

Butene-2 — *sec*-Butyl bromide

Sulfuric acid, another ionic and strongly acidic substance, also adds to alkenes. The acid is formulated as having one sulfur–oxygen

3.7



Sulfuric acid structure and resonance

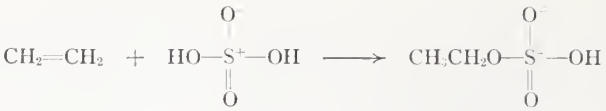
Sulfuric acid — Sulfate ion

double bond and one bond described as semipolar, since it is made up of one covalent bond and one ionic, or polar, bond. A second resonance structure is that in which the positions of the double bond and the semipolar bonds are reversed. Like a carboxylic acid, sulfuric acid contains an unsaturated atom carrying a hydroxyl group; in this case there are two hydroxyl groups. Thus the sulfate ion is a hybrid stabilized by resonance among several structures, three of which are formulated. The strongly acidic character of sulfuric acid is thus understandable.

Concentrated sulfuric acid (96%) adds readily to alkenes even at 0°. The product of addition to ethylene is ethylsulfuric acid, the

3.8

Addition to alkenes

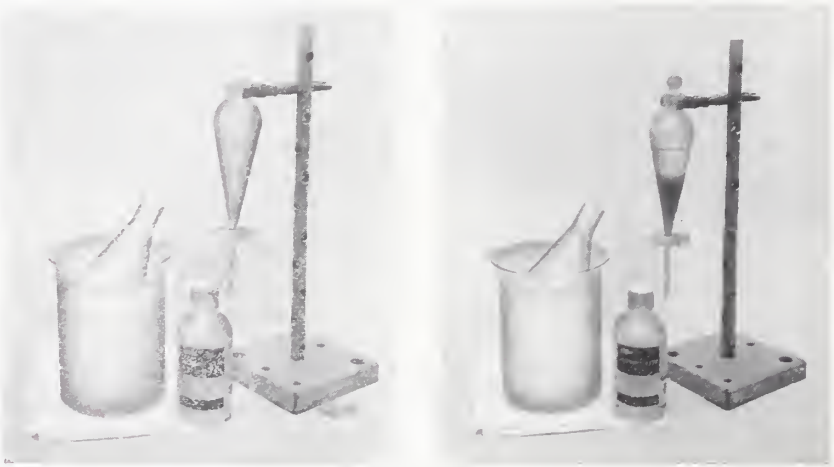


Ethylsulfuric acid

mono ester of a dihydroxy acid. The esters previously discussed are derived from an alcohol and an organic acid; this one is the ester of an inorganic acid. Ethylsulfuric acid retains one hydroxyl group and is a strong acid like sulfuric acid. Hence the product of the addition reaction is soluble in the reagent used to form it; it is also soluble in water. Alkanes are insoluble in sulfuric acid, and hence an alkane containing a little alkene as an impurity can be purified by treatment with this acid. Thus cyclohexane contaminated with a little cyclohexene is poured into a separatory funnel (a), ice-cold concentrated sulfuric acid is added, the funnel is stoppered and shaken

Purification of an alkane

Use of a seporatory funnel



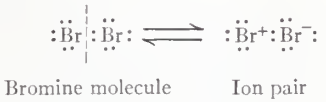
(a) (b)

thoroughly and let stand for the layers to separate (b). The heavier layer of sulfuric acid containing the ester resulting from addition to the cyclohexene is then run out, and the hydrocarbon layer is washed with water to remove traces of sulfuric acid adhering to the walls of the funnel and then dried. If the operation has been performed properly, the material will now give a negative test for unsaturation. The test is done by adding a sample to a dilute solution of bromine in carbon tetrachloride; if unsaturated material is present, it will discharge the color of bromine.

Test for unsaturation

3.9 Mechanism of Halogen Addition. — As noted in the preceding section, the fact that H^+Br^- catalyzes the addition of bromine to an alkene, coupled with the fact that H^+Br^- itself and $H^+O^-SO_2OH$ also add to alkenes, suggests that the addition of bromine involves an

ionic intermediate. Possibly the bromine molecule undergoes dissociation, or at least insipient dissociation, to an ion pair comparable to H^+Br^- by the following process:



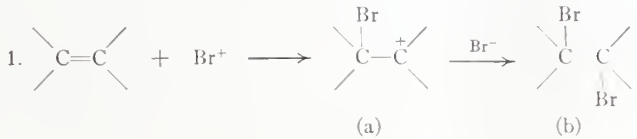
Bromine molecule Ion pair

Further inferences become possible from the results of extensive studies of the rates of halogenation reactions under different conditions made by a research group at University College, London, under the direction of C. K. Ingold. The conclusion seemed inescapable that addition of halogen is not a simple one-step process involving opening of the double bond and simultaneous joining of halogen atoms to the adjacent carbons, but that the halogen atoms are attached one at a time. The initial attack must then be by one member of the ion pair Br^+Br^-. A decision as to whether the positive (cation) or negative (anion) ion initiates the addition is reached by considering the analogous addition of H^+Br^- and $H^+O^-SO_2OH$; since Na^+Br^- and $Na^+O^-SO_2ONa$ do not add, the addition of the acids must initiate in an attack by the cation H^+. By analogy, the first step in bromine addition must be an attack at one of the unsaturated carbon atoms by the cation Br^+. Such a process would produce a transient intermediate (a) with the positive charge on the second carbon atom, a

3.10

A two-step process

Initial attack by Br^+



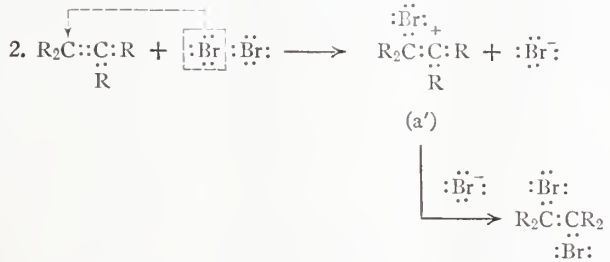
(a) (b)

Mechanism

carbonium ion. The carbonium ion then combines with Br^- with neutralization of the charge and formation of the dibromide (b).

The concept of the two-step reaction mechanism can be expressed alternatively in the electronic formulation 2. Here the same result is

3.11



(a′)

Alternative formulation

achieved without assumption of an initial ionization of the bromine molecule. Instead, one atom of this molecule retains the covalent

Electrophiles: Br^+, H^+

pair of electrons and becomes a bromide ion, Br^-, and the other accepts a pair of electrons from the double bond and becomes bonded to one of the carbon atoms. This electron-accepting, or electron-seeking, bromine atom is described as electrophilic, and bromine addition is described as an electrophilic addition because the initial step is an attack by an electron-seeking agent. The electrophilic agent can be regarded either as the electron-poor bromine atom of 2 or as the positive ion Br^+ of 1. Electrophilic addition of H^+Br^- to an alkene initiates in attack by the electrophile H^+.

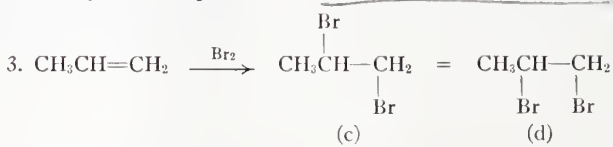
3.12

It will be noted from 2 that, in the intermediate carbonium ion (a′), the carbon carrying the positive charge is surrounded by only six electrons, and not by the usual eight required for stability. The ion is thus a highly reactive intermediate of only fleeting existence, and combines with bromide ion at a rate greater than the rate at which it is formed. It will be seen presently, however, that the concept of such an ionic intermediate helps greatly in understanding various facts about electrophilic additions.

3.13

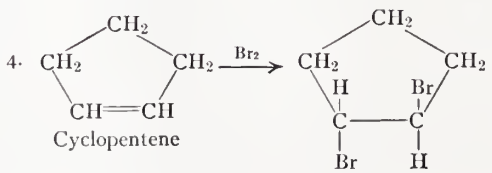
One fact is suggested in formulations 1 and 2 by writing the two bromine atoms of the final product as being on opposite sides of the molecule. The fact is that the two bromines do approach from opposite sides; one comes in from the front and the other from the rear. A possible explanation can be seen from formulation 1: the bromine atom of the carbonium ion (a) is electronegative, and hence repels Br^- and causes this ion to attack from the opposite side. The addition is, specifically, a *trans*-addition, which may or may not be evident from the identity of the product. Addition of bromine to propylene

trans-addition: bromines approach from opposite sides

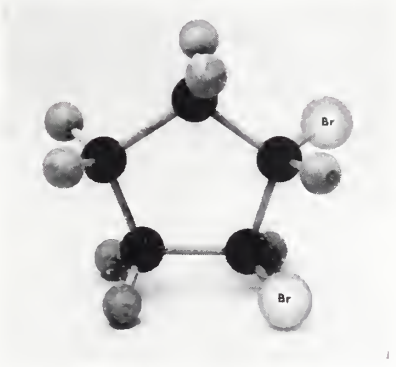


(3), whether it were *cis* or *trans*, would give the same product, because, by rotation about the single connecting bond, (c) is equivalent to (d). In ring compounds, however, rotation about a single bond is restricted by the ring, and *cis*- and *trans*-dibromides become a reality. In all cases studied, the initial product of bromine addition is the *trans*-dibromide. Bromine addition to cyclopentene is thus represented as in formulation 4. This formulation shows the *trans*-relationship of

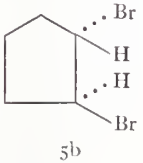
Rotation impossible



the two bromine atoms, and the model (5a) shows the actual orientation of the bromine and hydrogen atoms. The projection of the model



5a



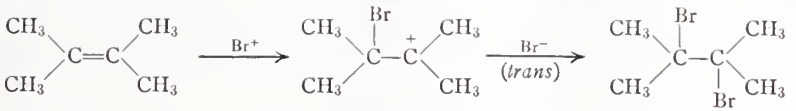
5b

trans-Dibromocyclopentane

is (5b); in this formula β-atoms projecting to the front are connected by full-line bonds, and α-atoms projecting to the rear are connected with dotted-line bonds. The structure and configuration (steric arrangement) are defined by the name 1α,2β-dibromocyclohexane.

Influence of Substituent Groups on Reaction Rate. — Alkenes vary considerably in the rate at which they add bromine (or chlorine, or iodine). Propylene, $CH_3CH{=}CH_2$, adds bromine twice as fast as ethylene. Tetramethylethylene, $(CH_3)_2C{=}C(CH_3)_2$, adds bromine at a rate fourteen times the rate of addition of bromine to ethylene. Thus methyl groups attached to one or the other of the two unsaturated

3.14



carbon atoms promote electrophilic attack, e.g., by Br^+. A methyl group on an unsaturated carbon atom thus, by an inductive effect, increases this atom's electron-availability, or negativity. From this evidence the methyl group is recognized as electron-repelling, or electron-releasing; a methyl group on an unsaturated carbon increases the electron density of the carbon atom and so makes it a more attractive site for attack by an electrophile such as Br^+ or H^+. A carboxyl group has the opposite effect; acrylic acid, $CH_2{=}CHCOOH$, adds bromine very slowly. The carboxyl group is thus recognized as having an inductive effect the opposite of that of a methyl group; it is electron-attracting, and hence decreases the electron-availability of an unsaturated carbon to which it is joined, with consequent decrease in its availability for attack by Br^+ or H^+.

Methyl group electron-repelling

Carboxyl is electron-attracting

3.15 Halogenation in Alkaline Solution. — In a neutral or acidic medium chlorine adds to ethylene to give ethylene dichloride, $ClCH_2CH_2Cl$. When the reaction is done in the presence of alkali, the product is $HOCH_2CH_2Cl$, a chlorohydroxy compound, or chlorohydrin. Treatment of ethylene chlorohydrin with strong alkali results in elimination of the elements of hydrogen chloride between the two functional

Hypohalite addition

$$CH_2{=}CH_2 + Cl_2 + NaOH \longrightarrow \underset{\text{Ethylene chlorohydrin}}{ClCH_2CH_2OH}$$

$$\underset{\text{Ethylene chlorohydrin}}{\overset{\displaystyle CH_2CH_2}{\underset{\displaystyle Cl\ \ OH}{|\quad|}}} \xrightarrow{NaOH} \underset{\text{Ethylene oxide}}{\overset{\displaystyle CH_2{-}CH_2}{\diagdown\ \diagup\ O}}$$

groups and production of ethylene oxide, a reagent of use in synthesis. Bromine in alkaline solution reacts similarly with alkenes to give bromohydrins. The reaction is regarded as a two-step process initiated by an attack by the electrophile Br^+, as in bromination. In an alkaline medium of high hydroxide ion concentration, the intermediate car-

Mechanism

$$\underset{\diagdown\ \diagup}{C{=}C} \xrightarrow{Br^+} \underset{\diagup\ \diagdown}{\overset{Br}{|}\ \overset{+}{C}{-}C} \xrightarrow{OH} \underset{\diagup\ \diagdown}{\overset{Br}{|}\ \ C{-}C} \qquad \underset{OH}{|}$$

bonium ion combines with OH^- in preference to Br^-. Where a stereochemical difference is detectable, the product is the *trans*-bromohydrin. The reaction is thus completely analogous to bromine addition.

3.16 HX-Addition to Alkenes. — An analogous two-step mechanism accounts for all facts known about the addition of H^+Br^- or $H^+O^-SO_2OH$ to alkenes. Thus addition of the former reagent to ethylene involves attack by the electrophile H^+ and combination

Electrophilic attack

$$CH_2{=}CH_2 \xrightarrow{H^+} CH_2{-}\overset{+}{C}H_2 \xrightarrow{Br^-} CH_2CH_2Br$$

of the resulting carbonium ion with bromide ion to form ethyl bromide. Ethylene adds hydrogen iodide even more readily but does not add hydrogen chloride, the least reactive of the halogen acids. However, ethylene is unique in this respect, for its higher homologs add hydrogen chloride under the same conditions (concentrated aqueous acid). The difference is easily explained. Butene-2, which adds the reagent, can

$$\underset{\text{Butene-2}}{CH_3CH{=}CHCH_3} \xrightarrow{H^+} CH_3CH_2{-}\overset{+}{C}HCH_3 \xrightarrow{Cl^-} \underset{\displaystyle Cl}{\underset{|}{CH_3CH_2CHCH_3}}$$

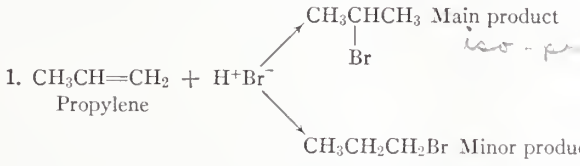
be regarded as the symmetrical dimethyl derivative of ethylene, and the electron-releasing methyl groups increase the electron density of

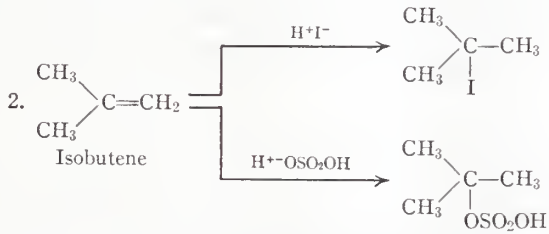
the unsaturated carbons and so enhance attraction for the electrophilic proton, or hydrogen ion.

Markownikoff Rule. — Butene-2, the example selected for the formulation just discussed, is symmetrical, and hence the product is the same whether addition of the unsymmetrical reagent is written in the manner shown or in the reverse order. With an unsymmetrical alkene such as propylene, where two products are possible, one of the two products usually is formed almost to the exclusion of the other. Thus propylene (1) adds hydrogen bromide almost exclusively to form isopropyl bromide, and *n*-propyl bromide is found in only minor amount. Isobutene (2) adds the unsymmetrical reagents

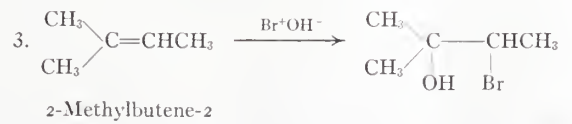
3.17

Examples of additions





hydrogen iodide and sulfuric acid exclusively in the manner shown to give *t*-butyl iodide and *t*-butylsulfuric acid. Bromine addition in alkaline solution can be thought of as involving the unsymmetrical reagent hypobromous acid, Br^+OH^-, and this adds in a specific way, as illustrated for 2-methylbutene-2 (3).



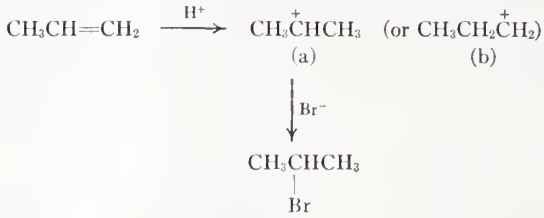
3.18

Statement of the rule

In 1869 the Russian chemist Vladimir Vassiliewitsch Markownikoff formulated an empirical rule which accurately summarized all facts known at the time. The Markownikoff rule states that, in the addition of H^+X^- or Br^+OH^-, the positive ion becomes attached to the unsaturated carbon carrying the smaller number of alkyl groups. Inspection of the examples cited above will show that the rule holds in each case. Subsequent to the formulation of the rule, a great many additional reactions were studied and found to conform to the usual pattern, and hence the rule became recognized as a useful guide for prediction of the outcome of previously unexplored reactions. A

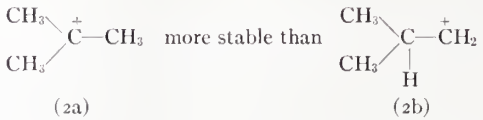
Theory of why the rule applies

theoretical interpretation of the rule became evident only with the development of modern concepts of reaction mechanisms. If the first step in the addition of H^+Br^- to propylene is an electrophilic attack by H^+, two different carbonium ions are possible, (a) and (b). Each ion has an electron sextet and is hence unstable, but an inductive

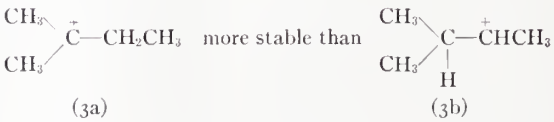


effect causes (a) to be at least more stable than (b). The effect is that in (a) the charged carbon carries two electron-releasing alkyl groups (methyl), which tend to neutralize the positive charge, whereas in (b) the charged carbon carries only one stabilizing alkyl group (ethyl). The ion (a) of superior stability is the one formed, and in the completing step bromide ion is attracted at the position carrying the charge. In the example below carbonium ion (2a) has three alkyl

Relative stability of carbonium ions



(2a) (2b)



(3a) (3b)

groups to neutralize the positive charge, while (2b) has only one such group (isopropyl) and is therefore less stable. In (3a) there are three stabilizing groups on the charged carbon, as compared to two in (3b). An empirically stated rule is no longer needed, for it is now possible to infer the mode of addition from knowledge of the mechanism of electrophilic additions and of the fact that alkyl groups are electron-releasing.

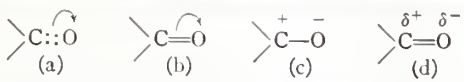
NUCLEOPHILIC ADDITION

3.19 *Definition*

A nucleophilic addition is the opposite of an electrophilic addition, namely one in which the initial attack at an unsaturated carbon is by a negative ion. This ion, an anion, is thought of as being attracted to the positive nucleus of carbon, and this concept is the basis for the name nucleophilic, or nucleus-seeking. Nucleophilic additions to unsaturated hydrocarbons are best considered from a background of the

main facts about nucleophilic additions to carbonyl compounds, particularly aldehydes and ketones. Because oxygen is a more electronegative element than carbon, the carbonyl group is partially polarized in the sense that oxygen is slightly negative and carbon slightly positive. The difference in electronegativity of the two elements causes a displacement of the shared electrons in the direction represented in (a) and (b) by curved arrows, or in the sense that the electron density around oxygen is greater than that around carbon.

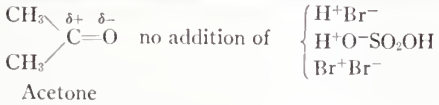
Partial polarization of carbonyl group



(a) (b) (c) (d)

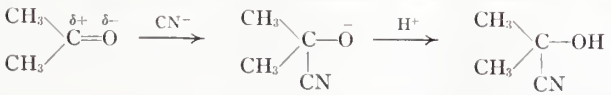
No electron transfer, or actual charge separation to form the semipolar bond (c), is implied, but rather an unequal sharing of electrons resulting in partial polarization. Partial ionic charges are indicated by the symbols $\delta+$ and $\delta-$, and hence the character of the carbonyl group can be expressed by formulation (d).

Acetone, a typical ketone, enters into none of the electrophilic 3.20



Acetone

additions characteristic of alkenes. The failure to react is understandable, because an analogous reaction would involve attack by a positive ion at the positively polarized carbon center, which would repel rather than attract the positive ion (attack by H^+ on oxygen would not be analogous to an alkene reaction). On the other hand, acetone adds reagents which do not add to alkenes and which evidently attack in a different way. One is hydrogen cyanide. That this substance does not add to alkenes the way H^+Br^- adds is perhaps because it is a weak acid and the hydrogen does not have a sufficiently developed positive character for electrophilic attack. The reason for its ability to add to acetone can be inferred from the structure of the product, a cyanohydrin. In this substance the cyanide group is attached to carbon, and hence it is reasonable to infer that the reaction



Acetone cyanohydrin

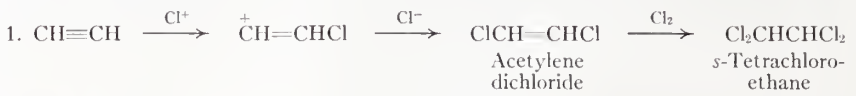
Mechanism of nucleophilic addition

which initiates addition is an attack by the negative cyanide ion at the positively polarized carbon of the carbonyl group. The nearby oxygen can accept the negative charge to form an anionic intermediate which can combine with a proton to form the cyanohydrin.

This is the accepted mechanism of nucleophilic additions; a number of other reactions of carbonyl compounds follow the same pattern.

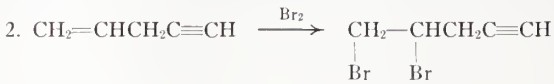
3.21 **Alkyne Additions.** — Alkynes, like alkenes, add halogens and hydrogen halides in reactions that initiate in attack by an electrophilic agent. For example, acetylene reacts with chlorine by the usual two-step mechanism (1) to form acetylene dichloride, which in turn adds a further mole of reagent to form *s*-tetrachloroethane (*s* stands for

Electrophilic additions



symmetrical), a useful solvent. Comparison of the rate of addition of the first mole of halogen to a triple bond with the rate of addition of the same halogen to a comparable double bond reveals the surprising fact that the triple bond is less reactive to electrophilic attack than the double bond. The difference is sufficiently great that a double bond can be selectively brominated in a molecule containing a triple bond (2). One would have thought that a triple bond, with its three

Less reactive than alkenes

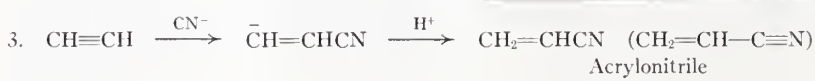


pairs of shared electrons, would be more, rather than less, susceptible to attack by a positive ion or electrophile. The apparent anomaly still awaits theoretical interpretation.

3.22 In line with the decreased reactivity of the triple bond to electrophilic attack, and equally mysterious, is the fact that alkynes show susceptibility to nucleophilic attack not shared by alkenes. Alkynes are intermediate between alkenes and carbonyl compounds in additive power. Thus one reagent, hydrogen cyanide, which adds to the carbonyl group of aldehydes and ketones also adds to the triple bond of alkynes. The reaction of hydrogen cyanide with acetylene is formulated as an attack on carbon by the negative cyanide ion, a nucleophile,

More reactive in nucleophilic additions

Addition of HCN

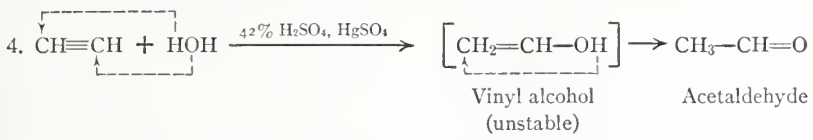


and combination of the resulting negative ionic intermediate with hydrogen ion (3). The product, acrylonitrile, is a valuable component for the manufacture of plastics and is produced on a huge scale by the reaction cited.

3.23 Alkenes do not react with hydrogen cyanide and they do not enter into a second addition characteristic of alkynes, namely catalytic hydration. The reaction involves addition to the triple bond of the elements of water, and in the case of acetylene it is accomplished by

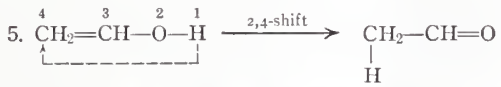
Addition of HOH

passing the gas into a hot solution of sulfuric acid containing mercuric sulfate as catalyst (4); the reaction involves a complex of the alkyne



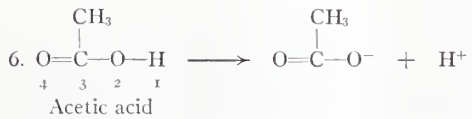
with the catalyst. The product initially formed, vinyl alcohol, is not stable and at once isomerizes to acetaldehyde by migration of hydrogen from oxygen to carbon and simultaneous shift of the double bond. Vinyl alcohol has a double-bonded carbon, or ene group, combined with a hydroxyl, or ol group, and it is conveniently described as an unstable enol. The migration of the hydroxylic hydrogen atom of the enol is an example of a general phenomenon. This hydrogen is a member of a special kind of system, C=C—O—H, which can be described in general terms as the system 4=3—2—1. The 1-atom is singly bound to the 2-atom and the 3-atom is doubly bound to the 4-atom. The isomerization of vinyl alcohol to acetaldehyde can thus

Vinyl alcohol an enol



be described as a migration of hydrogen in such a system from the 2- to the 4-position, or a 2,4-shift. The migration must be due to the presence of the 3,4-double bond, since the corresponding saturated compound, ethyl alcohol, undergoes no hydrogen shift. Hence hydrogen attached to the 2-atom is activated by the 3,4-double bond. The value of a generalized statement of the case is that it permits correlation with other phenomena. Thus acetic acid has the system O=C—O—H, with hydrogen at position 1 (6). That this hydrogen is activated by the 3,4-double bond is evidenced by the fact that it

2,4-Shift

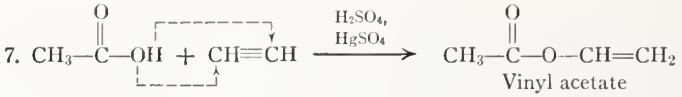


Analogous activation

tends to separate as a proton and produce the acetate ion. The unsaturated systems of (5) and (6) are different, and 3,4-double bond activation is manifested in one case in a migration and in the other by ionization, but a correlation between the two phenomena is nevertheless evident.

A further reaction analogous to catalytic addition of water is catalytic addition of acetic acid to acetylene (7). The product of addition, vinyl acetate, is not labile, like the parent vinyl alcohol, since the enolic hydrogen is replaced by an acetyl group, which has

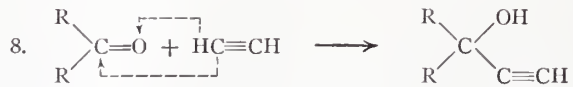
Addition of acetic acid



no tendency to migrate. Vinyl acetate manufactured by this method is a key material for production of vinyl resins.

3.25 In two other reactions acetylene functions as the entity H—A in an addition to an unsaturated compound. One involves addition of acetylene to the carbonyl group of a ketone (8) and is closely analogous to the addition of hydrogen cyanide to a ketone (8a). The two

Acetylene itself can add

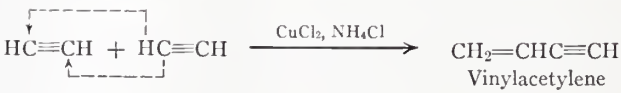


Compare:



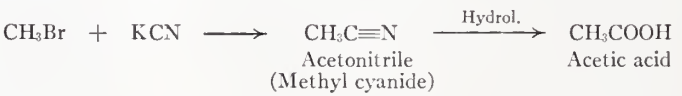
reagents are triple-bonded compounds of analogous structure and they are both weakly acidic. That acetylene can function both as acceptor for various H—A reagents (H—CN, H—OH, H—$OCOCH_3$) and as an H—A reagent itself, accounts for an interesting reaction in which acetylene adds to itself to form a dimolecular product, or dimer, vinylacetylene. The dimerization is effected by absorption

Self-addition



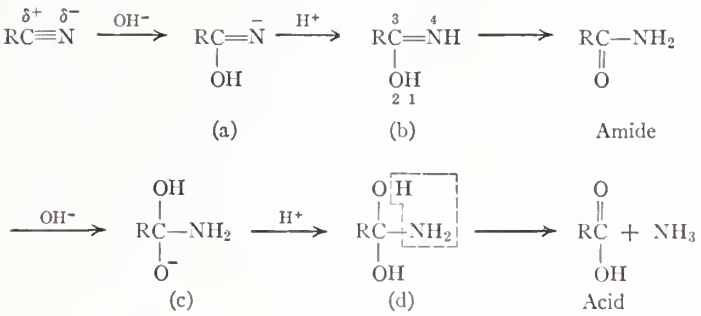
of acetylene gas in a solution of cuprous chloride and ammonium chloride in hydrochloric acid. Vinylacetylene is a key intermediate in the production of a superior synthetic rubber.

3.26 **Nitriles.** — Compounds of the type R—C≡N are called both nitriles and cyanides. Thus the product of addition of hydrogen cyanide to acetylene (3.22) is called acrylonitrile and that formed by addition of the same reagent to acetone (3.20) is known as acetone cyanohydrin. The simplest compounds of the class are made by reaction of potassium cyanide with an alkyl halide, for example, methyl bromide. The

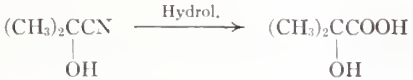


name methyl cyanide emphasizes the origin of the compound, but the name acetonitrile is usually used in emphasis of a characteristic reaction, hydrolysis. Acetonitrile is thus the nitrile that on hydrolysis

yields acetic acid. The hydrolysis of a triply bonded nitrile group is comparable to the catalytic hydration of an acetylenic triple bond, and hence extends the analogies already evident between H—C≡N and H—C≡CH. The reaction is interpreted as a nucleophilic attack



by OH^- at the positively polarized carbon to form an ion (a), which on acquisition of a proton affords an enol-like intermediate (b). A 2,4-hydrogen shift in (b) gives an amide, a product which can be isolated as an intermediate by moderation of the conditions of hydrolysis. Complete hydrolysis to the acid probably involves a second nucleophilic attack to give (c), acquisition of a proton (d), and elimination of ammonia. The synthesis and hydrolysis of nitriles is a



useful route to acids. Thus acetone cyanohydrin on hydrolysis affords α-hydroxyisobutyric acid (hydroxyl group in the α- or adjacent position to the carboxyl group).

SUMMARY

Reaction types: substitution ($ROH + HX \longrightarrow RX + H_2O$); addition [$O{=}C{=}O + HOH \rightleftharpoons O{=}C(OH)_2$]. Two types of shared electrons: sigma, for bonding (single bond; one of the two pairs in a double bond); pi (the other pair in a double bond), responsible for addition reactions.

Alkanes. No pi electrons, hence no addition reactions, general lack of reactivity. *n*-Alkanes inert to H_2SO_4, NaOH, HNO_3, $KMnO_4$. No reaction with Br_2, Cl_2 in dark. Light-catalyzed substitution: $C_6H_{14} + Br_2 \longrightarrow C_6H_{13}Br + HBr$. Light splits halogen molecules to halogen atoms (free radicals, odd electrons). Homolysis: $Cl{:}Cl \longrightarrow Cl\cdot + \cdot Cl$. Attack by radical: $Cl\cdot + RH \longrightarrow HCl + R\cdot$. Production of chloroalkane with regeneration of radical: $R\cdot + Cl_2 \longrightarrow RCl + Cl\cdot$. Free-radical reactions generally promoted by light, heat, or peroxide ($RO{:}OR \longrightarrow 2\,RO\cdot$). *n*-Pentane and isopentane attacked at random positions in thermal chlorination (200°) in dark to chloropentane mixture (solvent, conversion to alcohol mixture).

Cracking = decomposition at 500°. Homolysis of carbon–carbon bond to give two free radicals; hydrogen transfer to form an alkene and an alkane. Combustion of gasoline involves cracking to radicals which combine with the oxygen molecule, which is a diradical.

Alkene Additions

Halogen addition: $CH_2{=}CH_2$ (gas) + Cl_2 ⟶ $ClCH_2CH_2Cl$ (ethylene dichloride, liquid). Olefin (oil-former) = alkene. Addition rapid in dark. Catalyzed by H^+Br^-, which itself adds to give CH_3CH_2Br. Sulfuric acid (one double bond, one semipolar bond) also adds: $CH_2{=}CH_2 + H^+O^-SO_2OH$ ⟶ $CH_3CH_2OSO_2OH$, ethyl sulfuric acid. The product, an ester, soluble in H_2SO_4. A liquid alkane (e.g. hexane), being insoluble in and inert to H_2SO_4, is freed of alkene impurities by shaking with cold H_2SO_4.

Mechanism of halogen addition. Analogy to H^+Br^- addition suggests that Br_2 adds as Br^+Br^-. Reaction-rate studies (Ingold) show the two halogens to be attached one at a time. Inference that in addition of H^+Br^- and $H^+O^-SO_2OH$ first step is attack by H^+ and hence that Br^+Br^- addition involves initial attack by Br^+. Mechanism: attack by Br^+ (an electrophile = electron-seeking) to form carbonium ion and Br^-, approach of Br^- from opposite side to produce dibromide. Electronic formulation shows charged carbon of the carbonium ion to be electron-deficient (6 electrons). Addition to cyclopentene establishes the fact of *trans*-addition: one bromine to the rear (α, dotted line), the other to the front (β, full line).

Reactivity increases from $CH_2{=}CH_2$ to $CH_3CH{=}CH_2$ to $(CH_3)_2C{=}C(CH_3)_2$, therefore methyl groups increase affinity for Br^+ (increase negativity of unsaturated carbon atoms; increase electron density at these sites). Methyl recognized from this inductive effect as an electron-repelling (electron-releasing) group. Carboxyl (e.g. in acrylic acid, $CH_2{=}CHCOOH$) decreases rate of bromine addition, is therefore electron-attracting.

Hypohalite addition (halogen in alkaline solution): attack by electrophile X^+, as in halogen addition, combination with OH^- to form XCH_2CH_2OH (ethylene chlorohydrin or bromohydrin). Is a *trans*-addition. Ethylene oxide from ethylene chlorohydrin and alkali.

Markownikoff rule: in the addition of H^+Br^- or Br^+OH^- to an unsymmetrical alkene, the positive ion becomes attached to the carbon having the smaller number of alkyl groups. Theoretical explanation: the direction of addition depends upon the relative stability of the two possible carbonium ions; the electrophile attacks the carbon with the fewer alkyl groups because the charge at the second carbon is then stabilized by the electron-releasing alkyl groups.

Nucleophilic Addition

A nucleophile, a negative ion (positive-nucleus-seeking). Attacks carbonyl group because this is polarized and carries partial positive charge on carbon. Addition of H^+CN^- to acetone gives acetone cyanohydrin, $(CH_3)_2C(OH)CN$. Mechanism: attack by CN^- at carbon with acceptance of the charge by oxygen; combination with a proton.

Alkynes. In electrophilic additions triple bond less reactive than double bond; can selectively add Br_2 to double bond of a compound also having a triple bond. Acetylene adds Cl_2 to form acetylene dichloride and then *s*-tetrachloroethane,

$$CHCl_2CHCl_2.$$

Nucleophilic addition of HCN to acetylene to form acrylonitrile, $CH_2{=}CHCN$. Mechanism as in addition of HCN to acetone. Catalytic addition of water to triple bond:

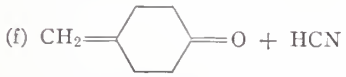
$$CH{\equiv}CH \longrightarrow CH_2{=}CH{-}OH \text{ (vinyl alcohol)}$$
$$\longrightarrow CH_3CH{=}O \text{ (acetaldehyde)}.$$

Vinyl alcohol an unstable enol with the system 4═3—2—1. Isomerization to acetaldehyde described as a 2,4-shift (atom in position 1 shifts from atom 2 to atom 4, and bond moves between 2 and 3). Analogy of vinyl alcohol to acetic acid. Addition of acetic acid to acetylene gives stable product, vinyl acetate.

Addition of acetylene to carbonyl group of a ketone. Analogous to addition of HCN. Self-addition of acetylene to give the dimer vinylacetylene.

Nitriles, $RC{\equiv}N$ (also called cyanides), from $RX + KCN$. Hydrolysis to an amide, $RCONH_2$, then to an acid. Analogy to the hydration of acetylene.

PROBLEMS

1. Do the relative proportions of isomers formed in the thermal chlorination of the pentanes (3.4) correspond to expectations from the law of probability?
2. Suggest an initial product that might arise by cracking an alkane to radicals in the presence of molecular oxygen.
3. What products would you expect to result from the careful addition of only one mole of bromine to each of the following hydrocarbons:
   (*a*) $(CH_3)_2C{=}CHCH_2CH{=}CH_2$
   (*b*) $CH_3CH{=}CHCH_2C{\equiv}CCH_3$
4. Predict the chief products of each of the following reactions:
   (*a*) $CH_2{=}CHCH_2Br$ (allyl bromide) + Br_2
   (*b*) $(CH_3)_3CCH{=}CH_2 + H_2SO_4$
   (*c*) $CH_3CH{=}C(CH_3)CH_2CH_3 + Br_2 + NaOH$
   (*d*) $CH_3CHCH_2CCH_3$ (with a double bond between the two carbons) + HI
   CH_2CH_2CH
   (*e*) Cyclohexene + Br_2
   (f) 
   (*g*) $CH_3CH{=}CHCH_2C{\equiv}CH + (CH_3)_2C{=}O$
5. The catalytic hydration of an unsymmetrical alkyne follows the Markownikoff rule (OH goes to the carbon richer in alkyl groups). Deduce the structure of the product resulting from hydration of vinylacetylene (3.25).

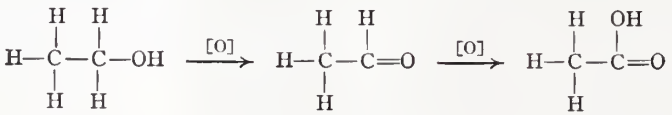
CHAPTER 4

OXIDATION AND REDUCTION

4.1 **Oxidizable Types.** — Whereas saturated hydrocarbons are inert to such chemical oxidizing agents as potassium permanganate, sodium dichromate, or chromic acid, these reagents oxidize unsaturated hydrocarbons, that is, alkenes and alkynes. The reagents also oxidize primary and secondary alcohols as well as aldehydes, and consideration of the reactions involved will facilitate understanding of oxidations of unsaturated hydrocarbons.

Unsaturated hydrocarbons, RCH_2OH, R_2CHOH, $RCHO$

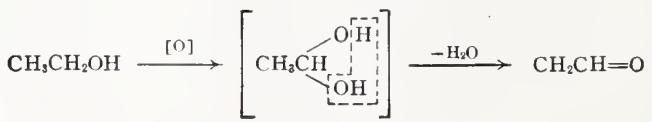
4.2 **Oxidation of Alcohols and Aldehydes.** — The fact that ethyl alcohol is easily oxidized whereas ethane is not, shows that the presence of oxygen in a molecule confers susceptibility to further oxidation. In ethyl alcohol one of the two carbon atoms is linked to oxygen, and hence is already oxidized, while the other is joined to hydrogen and carbon and corresponds to the carbon atoms of the inert ethane; hence oxidizing agents attack the molecule at the former, rather than the latter position. The initial oxidation product is acetaldehyde, which on further oxidation is attacked in the already oxidized part



Ethyl alcohol — Acetaldehyde — Acetic acid

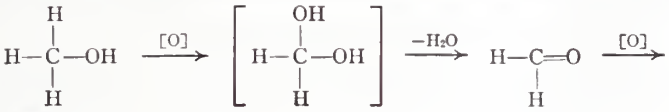
of the molecule and yields acetic acid as an end product resistant to further attack. Since the latter reaction consists in replacement of a hydrogen by hydroxyl, or hydroxylation of an oxidized carbon, it is reasonable to assume that the same process is involved in the oxidation

Hydroxylation of an oxidized C

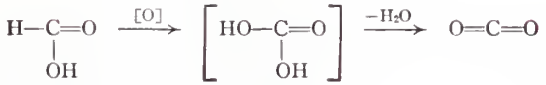


Unstable gem-diol

of ethyl alcohol to acetaldehyde. The initial step would then give the 1,1-dihydroxy, or 1,1-diol, derivative of ethane, a type known as a *gem*-diol, from the Latin *gemini*, meaning twins, since two hydroxyl, or ol, groups are twinned on the same carbon. The formula is written in brackets because *gem*-diols are unstable and are prone to lose water to form a carbonyl group. Loss of water in this instance affords acetaldehyde, the oxidation product actually formed. Thus both steps leading from ethyl alcohol to acetic acid can be interpreted as involving the same initial hydroxylation reaction. Acetic acid is stable to oxidation, though it contains a highly oxidized carbon atom, because this atom carries no hydrogen; carboxylic acids are the end products of oxidation of all higher primary alcohols, RCH_2OH. Oxidation of methanol may proceed to the stage of formaldehyde through an intermediate *gem*-diol; the next product is formic acid, HCOOH, and this, unlike acetic acid, still possesses a hydrogen atom on the oxidized carbon



Methanol — Formaldehyde

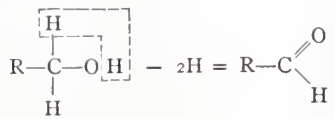


Formic acid

Formic acid unique

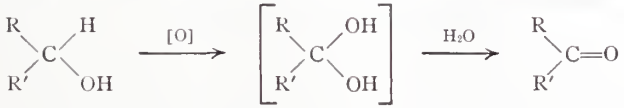
and is oxidized further. Replacement of the specially situated hydrogen by hydroxyl gives carbonic acid, an unstable diol which decomposes to carbon dioxide and water.

The behavior of ethyl rather than methyl alcohol is generally typical of primary alcohols, for such alcohols on oxidation yield aldehydes initially and then acids. Formally, the oxidation of a primary alcohol to an aldehyde can be described as the removal of two hydrogen — 4.3



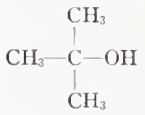
atoms, or a dehydrogenation; the word aldehyde is thus derived from alcohol dehydrogenated.

A secondary alcohol can undergo replacement by hydroxyl of the — 4.4



Secondary alcohol — Ketone

lone hydrogen on the oxidized carbon, followed by loss of water from the *gem*-diol with production of a ketone, and this product is the stopping point for normal oxidation. Thus permanganate oxidation of isopropyl alcohol gives acetone, and acetone is sufficiently resistant to further oxidation to be employed as solvent in permanganate oxidations of other substances. Tertiary alcohols, for example *t*-butyl

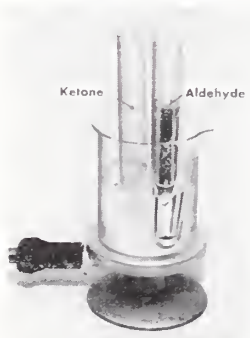


t-Butyl alcohol

alcohol, lack hydrogen on the oxidized carbon and hence are not vulnerable to oxidation.

4.5 ——— ***Silver mirror test***

The fact that aldehydes are oxidizable and ketones are not forms the basis for a simple test to distinguish between them, the silver mirror test. The test reagent is prepared by adding ammonia to an aqueous solution of silver nitrate; a transient precipitate of silver hydroxide dissolves to give a colorless solution of the complex silver ammonium ion (1). An aldehyde added to the solution is oxidized



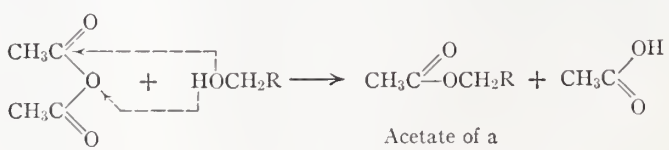
1. $Ag^+NO_3^- + 3\,NH_3 + H_2O \longrightarrow Ag(NH_3)_2^+OH^- + NH_4^+NO_3^-$
2. $RCHO + Ag(NH_3)_2^+OH^- \longrightarrow RCOO^-NH_4^+ + Ag + NH_3$

to the acid, which forms the ammonium salt, and the complex silver ammonium ion is reduced to metallic silver, which deposits on the walls to form a mirror (2). A ketone produces no comparable change. Thus if an alcohol is oxidizable to a carbonyl compound that gives a negative silver mirror test, the alcohol is recognized as secondary.

4.6 ——— ***Permanganate test***

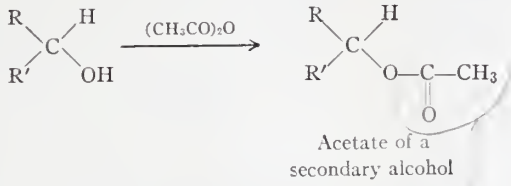
A test to determine whether a substance is oxidizable or not is easily done with permanganate because of the strong purple color: an oxidizable substance rapidly discharges the color of a solution of permanganate in dilute sulfuric acid and is thereby recognized as being either a primary or a secondary alcohol, an aldehyde, or an unsaturated hydrocarbon. It is possible by another simple test to distinguish the alcohol types from the other two types. This is by the reaction of acetylation. A primary alcohol reacts with acetic anhydride in the manner formulated; the anhydride bond is ruptured

Acetylation



Acetic anhydride — Acetate of a primary alcohol

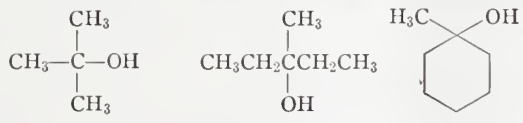
and the —OCH_2R group linked to carbon and H— linked to oxygen. The products are thus the acetate of the primary alcohol and acetic acid. Acetates are esters and are hydrolyzable to the original alcohol and acetic acid. Secondary alcohols are also acylable, and the hydroxylic hydrogen thus replaceable by the acetyl group. The hydroxylic hydrogen is involved in the oxidation of a primary or secondary alcohol to a carbonyl compound, and hence the acetates of primary and secondary alcohols are not oxidizable. Thus a substance which decolorizes permanganate, but which on treatment with acetic anhydride gives a product with which the permanganate test is negative, is recognized as either a primary or secondary alcohol. Application of the silver mirror test to the initial product of oxidation of the unacetylated material will distinguish between a primary and a secondary alcohol.



Acetate of a secondary alcohol

Acetylation prevents oxidation

Although incidental to the discussion of oxidation, it is of interest that tertiary alcohols are not acylable by the procedure ordinarily used. 4.7



Not acylable

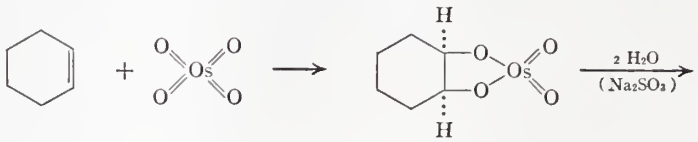
Tertiary alcohols not acylable

The failure to react with acetic anhydride seems to be due to a spatial effect, or steric hindrance. Three alkyl groups, or a combination of alkyl groups and ring residues, crowd the space around the carbon of the alcoholic function and prevent attack of the hydroxyl group by the reagent. The inertness to acetylation is thus due to a structural feature different from that causing tertiary alcohols to be inert to oxidation. Tertiary alcohols and alkanes, both inert to permanganate, can be distinguished from the fact that the alcohols are soluble in concentrated sulfuric acid and the hydrocarbons are insoluble.

Oxidation of Unsaturated Compounds. — Both double and triple bonds are points of vulnerability to oxidation by permanganate and other oxidizing agents. However, oxidation of alkynes presents no points of general interest and will not be discussed. Alkenes decolorize permanganate in dilute sulfuric acid and are distinguishable 4.8

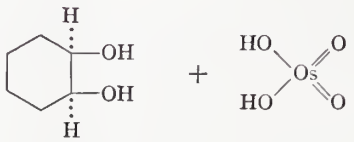
from alcohols by the fact that the test remains positive after treatment with acetic anhydride. They are distinguishable from aldehydes from the fact that they give a negative response in the silver mirror test. A permanganate oxidation of an alkene can proceed to various stages, depending upon the amount of reagent used and the conditions, but the first step of the process is exactly the same as the first step in oxidation with osmium tetroxide, a reagent which is incapable of carrying the oxidation beyond the initial step. This simpler reaction will thus be considered first.

4.9 **Osmium Tetroxide Hydroxylation of Alkenes.** — Osmium tetroxide, OsO_4, is a colorless crystalline solid melting at 40° and readily soluble in ether. On addition of cyclohexene to an ethereal solution of the reagent, a reaction product separates as a black precipitate. This substance is a cyclic osmate ester of the structure shown; it



Osmate ester

Cyclic intermediate

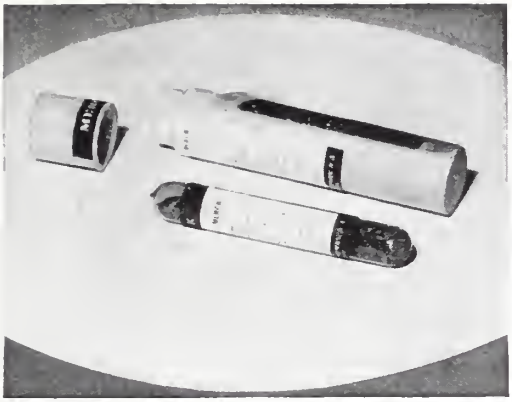


cis-Cyclohexane-1,2-diol

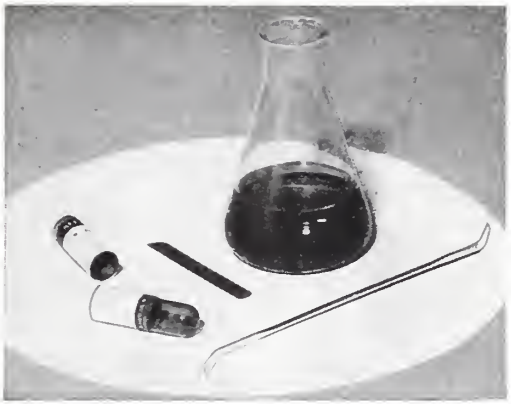
arises from simultaneous opening of the carbon–carbon double bond of the alkene and of the two double bonds of the metal oxide. The black ester is then hydrolyzed, with use of sodium sulfite as catalyst, and the product is *cis*-cyclohexane-1,2-diol (the hydroxyls are β, or to the front, and the hydrogens α, or to the rear). The five-membered ring of the osmate ester can be formed only in the *cis*-orientation and hence the reaction product is necessarily the *cis*-diol. Thus the ultimate result of osmium tetroxide hydroxylation is a *cis*-addition. Whenever a reaction is free to follow either a *cis*- or *trans*-course, the course normally taken is *trans*-addition. *cis*-Addition occurs only when the reaction involves a cyclic intermediate, which is of necessity *cis*-oriented, as in the example cited.

cis-Addition

4.10 Practical aspects of the reaction are interesting. Osmium tetroxide is an expensive reagent, costing over ten dollars per gram. Furthermore, the molecular weight is so high (254.20) in comparison to that



(a)



(b)



(c)

of cyclohexene (82.14) that 1 g. of osmium tetroxide is equivalent to only 0.32 g. of cyclohexene. Since cyclohexene is much less expensive, an excess of hydrocarbon is used to insure complete utilization of the precious metal oxide. Osmium tetroxide is supplied in sealed glass ampoules (a); each contains 1.0 g. and is packed in a wooden case with a taped-on steel scorer with a filing edge. The ampoule is scored in the middle, broken (b), and the crystals of oxide are scraped out into a flask and dissolved in ether. With a capillary dropping tube that has been calibrated and marked at the 1-ml. level with a rubber band, 1 ml. of cyclohexene is added (c). A black precipitate forms at once but remains partly in suspension, even during several hours while the mixture is let stand to insure complete reaction. The ether and excess cyclohexene are removed by evaporation on the steam bath and the black osmate ester is heated for several hours with aqueous-alcoholic sodium sulfite to effect hydrolysis to *cis*-cyclohexane-1,2-diol.

4.11

Melting point determination

The quality of the sample can be judged from the melting point, which can be determined with the apparatus shown in Fig. 4.11. A small sample is scraped into the open end of a tiny capillary tube sealed at the bottom, and the sample is caused to drop to the closed end by the vibration produced by light stroking with a file. The capillary tube is then attached to the stem of a thermometer with a rubber band. The thermometer is fitted by means of a cut-away cork into a heating flask containing paraffin oil, and heat is applied carefully so that the temperature rises at a slow, steady rate. One watches both the sample in the capillary and the thermometer reading, and records the temperature at which melting begins and that at which a

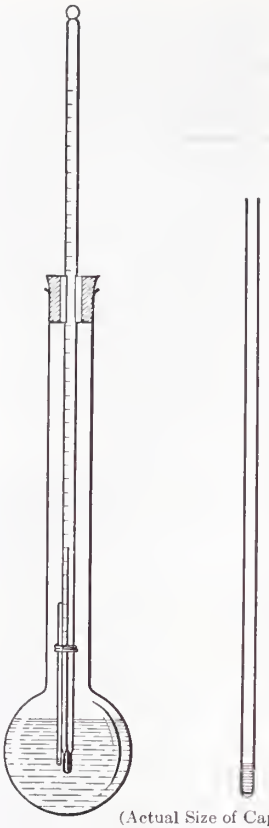


FIG. 4.11.— Determination of Melting Point

Variations in recorded melting points

clear melt results. In the experiment cited the melting point found was 97–98°. Consultation of the chemical literature shows that *cis*-cyclohexane-1,2-diol has been prepared in a number of laboratories by a variety of methods. Most investigators record a melting point of about 98°, close to that found in the present experiment, but melting points as low as 93° and as high as 99–100° have also been reported. Evidently the samples varied somewhat in degree of purity, or else there was some variation in accuracy of determination of melting point or in the accuracy of the thermometers used for the determinations. The deviations would seem of minor importance were it not that *trans*-cyclohexane-1,2-diol is reported to have the melting point of 104°, which is close to some of the reported values for the *cis*-isomer. Since impurities in a sample always lower the melting point, the high melting points reported for the *cis*-isomer are probably more reliable than the lower values.

4.12 ——— *Mixed melting point determination*

A sure way of establishing identity of the product of osmium tetroxide hydroxylation of cyclohexene is by the method of mixed melting point determination. A sample of authentic *cis*-cyclohexane-1,2-diol is prepared by one of the unambiguous methods reported in the literature, or else a sample is secured from a chemist whose papers show that the compound was prepared in his laboratory, and small piles of the new sample and the authentic sample are scraped together with a spatula and thoroughly mixed. The mixture is then introduced into a melting point capillary. The melting point of the mixture is then observed, and if it is essentially the same as that of the two components, or intermediate between them, they can be declared identical. If the mixture melts at a temperature lower than either component, the components are recognized as nonidentical. *cis*-Cyclohexane-1,2-diol melts at a temperature (98°) not far from the melting point of *trans*-cyclohexane-1,2-diol (104°), but mixtures of the two substances melt at temperatures significantly below 98°; one isomer depresses the melting point of the other. The same is true

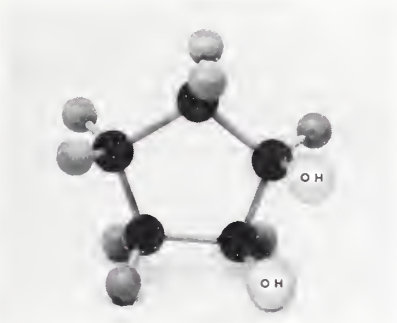
for any pair of compounds that happen to have melting points in the same range: a depression in melting point on admixture establishes nonidentity; absence of a melting point depression is evidence of identity. The melting point of a substance affords a useful index of its purity, since any extraneous contaminant produces a melting point depression. As a sample is repeatedly crystallized, the melting point becomes higher and sharper, that is, the temperature range is smaller, and eventually reaches a constant level.

Evidence of identity or nonidentity

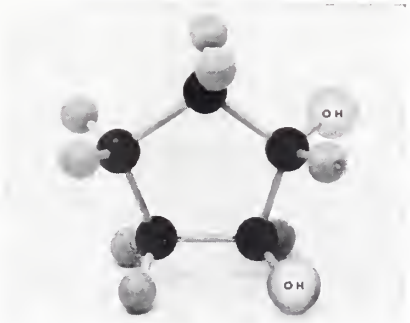
Of the isomer pairs just discussed, the cyclohexane-1,2-diols, the *trans*-isomer melts only a few degrees higher than the *cis*-isomer. The difference is in the usual direction but not so pronounced as is usually found. *trans*-Isomers are more symmetrical, or better balanced, than *cis*-isomers, and the resultant greater stability usually is reflected in significantly higher melting points. The isomeric cyclopentane-1,2-diols, whose melting points are shown under the photographs of models, are more typical.

4.13

trans-Isomer has the higher m.p.



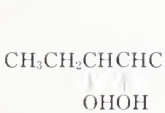
cis-Cyclopentane-1,2-diol
M.p. 30°



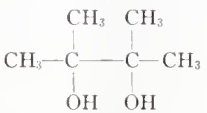
trans-Cyclopentane-1,2-diol
M.p. 55°

vic-Glycol Cleavage. — The above dihydroxy compounds can be described in general terms as 1,2-diols, but this designation may not apply to open-chain compounds of the same type, for example, I and II. Another name for a diol is glycol, and the specific type of glycol

4.14



I



II

in which the hydroxyl groups are on adjacent carbons is called a *vic*-glycol (hydroxyls in the same vicinity). Compounds I and II are *vic*-glycols, and so are the cyclopentane- and cyclohexane-1,2-diols.

Definition of vic-glycol

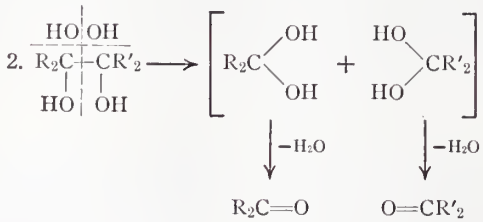
vic-Glycols are distinguished from ordinary alcohols, and even from glycols in which the hydroxyl groups are not on adjacent carbon atoms, in being susceptible to oxidative cleavage of the carbon–carbon

4.15

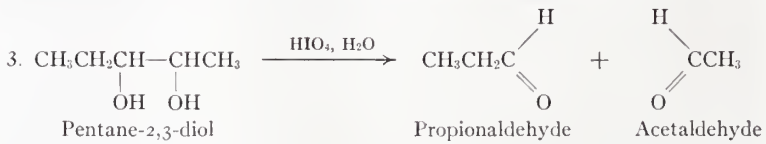
bond connecting the hydroxylated carbon atoms. This bond between oxidized carbon atoms is thus a weak one. To effect *vic*-glycol cleavage without further oxidation of the initial products, it is necessary to use an oxidizing agent of a specific type exemplified by periodic acid, HIO_4. This reagent is soluble in water and not in organic solvents, and hence the oxidation is done in aqueous solution or in a solvent mixture containing water. The reaction is most easily interpreted by imagining it to involve generation of hydroxyl radicals as in (1) and fission of the carbon–carbon bond by hydroxylation of each carbon

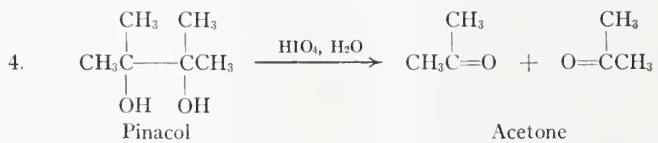


Cleavage to carbonyl compounds



atom (2). Each initial product of fission is an unstable *gem*-diol and water is eliminated spontaneously with formation of a carbonyl group. One mole of periodic acid (in water) thus cleaves the *vic*-glycol to two carbonyl-containing fragments. Whether each fragment is an aldehyde or a ketone is determined by the structure of the starting material. Pentane-2,3-diol on periodic acid cleavage affords equivalent





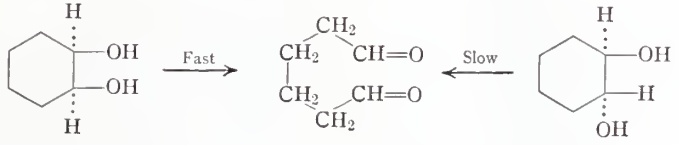
quantities of propionaldehyde and acetaldehyde (3). Pinacol (4) yields two moles of acetone. Thus when the hydroxylated carbon of the glycol carries a hydrogen atom the fragment derived from it is an aldehyde, but if it carries two alkyl groups the fragment is a ketone.

4.16 *Determination of reaction rate*

The rate of a glycol cleavage reaction is easily determined. Solutions of the glycol and of periodic acid are adjusted to a convenient temperature that can be kept constant during the oxidation; the solutions are then mixed and the time recorded. A 1-ml. sample of

solution is withdrawn at once with a pipette and run into a flask containing a measured volume of standard acidic potassium iodide, and the iodine liberated is titrated with standard sodium thiosulfate solution. From the result the periodic acid content of the 1-ml. sample is calculated; in the initial determination this value should represent close to the maximum possible. Further 1-ml. samples are removed at regular intervals and the consumption of periodic acid thus determined as a function of time. The most interesting finding of such reaction rate studies is that, in cyclic compounds where *cis* and *trans* isomerization is possible, *cis*-glycols are cleaved very much faster than *trans*-glycols. The difference is so striking that, if a pair of isomers can be shown to be a *cis-trans vic*-glycol pair, the relative rates of glycol cleavage can be used to establish which is *cis* and which *trans*. Note that although *cis*- and *trans*-cyclohexane-1,2-diol react

cis-Glycol cleaved faster than trans

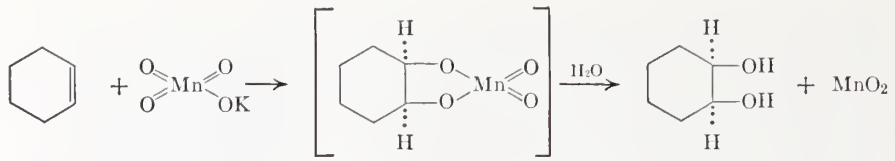


cis Adipaldehyde *trans*

at different rates they give the same product, a dialdehyde. The greater reactivity of the *cis*-isomer may mean that the reaction involves a cyclic intermediate in which both hydroxyl groups are bound to the reagent and that this is formed most easily when the two hydroxyls are close to each other. The hydroxyl groups of a *vic*-diol must both be free, for neither a mono- nor a diacetate is cleaved by periodic acid.

Permanganate Oxidation of Alkenes. — Potassium permanganate is a powerful reagent capable not only of hydroxylating a double bond, like osmium tetroxide, and of cleaving the resulting *vic*-glycol, like periodic acid, but also of oxidizing an aldehyde to an acid. It is difficult to control the oxidation to the stage of *vic*-glycol formation and impossible to stop it at the stage of an aldehyde. By use of just one oxygen equivalent of permanganate in a very dilute aqueous solution at 0–5°, alkenes can be oxidized to *vic*-glycols in yields which normally are low, but which are nevertheless adequate for preparative purposes; glycols are thus available at much less expense and effort than by use of osmium tetroxide. Where *cis-trans* isomerism is possible, permanganate, like osmium tetroxide, yields *cis*-glycols. It seems likely that a cyclic manganate ester is an intermediate (1), although such a substance has not been isolated. When the reaction is done in aqueous solution, a manganate ester if formed appears to be

4.17

1. 

C_6H_{10} Manganate ester

soluble in water and very easily hydrolyzed, and hence affords no protection to the *cis*-glycol. The balanced equation (2) appears to represent the ideal reaction. It will be noticed that potassium hy-

2. $3\ C_6H_{10} + 2\ KMnO_4 + 4\ H_2O \longrightarrow 3\ C_6H_{10}(OH)_2 + 2\ KOH + 2\ MnO_2$

droxide is a reaction product and hence that in an oxidation commenced in neutral water solution the mixture becomes increasingly alkaline as the reaction proceeds. If this effect slows down the reaction, it can be counteracted by addition of acetic acid.

4.18 *cis*-Cyclohexane-1,2-diol was prepared for the first time in 1878 by Markownikoff at the University of Moscow by the reaction under discussion in 24% yield. A demonstration of this preparation, with modern equipment and with some modifications in the procedure, is shown in the photographs (see also front cover). Cyclohexene (16.4 g.)

Permanganate oxidation



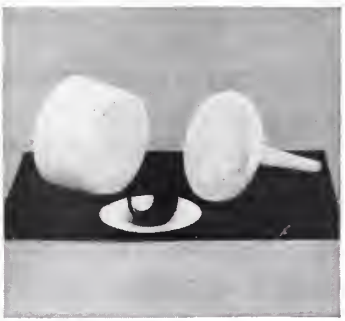
and water (700 ml.) are placed in a 2-liter three-necked flask equipped with a stainless steel stirrer mounted in a ball bearing; vigorous stirring is required to produce a near-emulsion of the insoluble hydrocarbon. The flask is cooled in a frequently stirred bath of ice, water, and salt to keep the temperature close to 0° during the mildly exothermic oxidation. A solution of permanganate (21.2 g. in 300 ml. of water) is run in from a separatory funnel by drops, and the rate of flow is adjusted so that the addition will be complete in about one hour. Each drop of solution produces only a fleeting purple coloration with rapid change to the brown color of manganese dioxide. At the end of the addition the apparatus is disassembled and the flask heated

on the steam bath for one half hour to coagulate the very finely divided manganese dioxide and hasten filtration of the alkaline solution.

The mixture is then filtered by suction onto a Büchner funnel with a porous disc over which a circle of filter paper is placed and then moistened so that it will be pulled down to a tight fit. The funnel illustrated is made of polyethylene plastic and can be separated into two parts for ease of cleaning; it is supported in the mouth of the

4.19





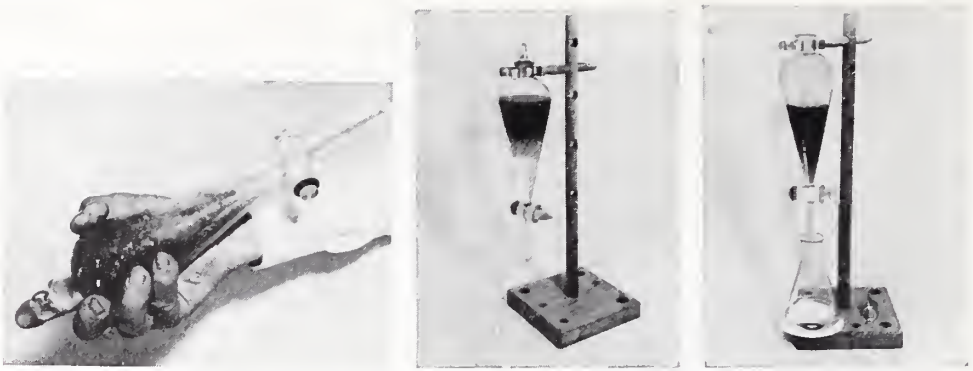
Suction filtration

filter flask with a Neoprene adapter. A trap to prevent a suck-back from the suction pump is equipped with a section of thin-walled tubing closed with a spring clothespin for release of pressure and also to function as a pressure gauge. The brown filter cake is washed well with water, and the flask is emptied and rinsed into a beaker. For neutralization of the alkali without danger of adding an excess of a possibly destructive mineral acid, pieces of dry ice are added until indicator paper shows that the pH has been reduced from 12 to about 9.

The solution is then boiled down over a free flame to a volume of 150 ml., as estimated by comparing the level with that in a duplicate beaker into which 150 ml. of water has been measured. The concentrated solution containing potassium bicarbonate and organic reaction products is cooled, poured into a separatory funnel, and extracted with an organic solvent immiscible with water. Markownikoff used ether, but chloroform ($CHCl_3$) seems more appropriate for a reason which will become apparent. After addition of chloroform, the mixture is shaken very vigorously (a) and let stand for separation of the layers (b, separation nearly complete). It is pleasant to find that the brown color all stays in the water layer and that the extract is colorless. When separation is complete, a receiving flask is put in place and the stopcock is opened to let the lower chloroform layer

4.20

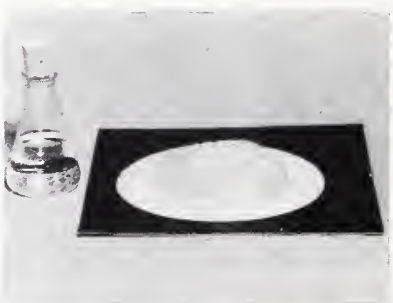
Extraction with chloroform



(a) (b) (c)

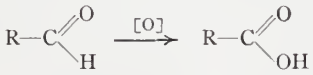
run in, and as the interface moves into the narrow part of the funnel the rate of flow is decreased so that the stopcock can be closed the moment the water phase is about to enter the funnel (c). *cis*-Cyclohexane-1,2-diol is so very soluble in water that a single extraction removes only a small fraction of the product. In the experiment demonstrated, twelve extractions were made. However, with chloroform as the extraction solvent repeated extraction proceeds rapidly. After the first chloroform extract has been drawn off (c), another portion of chloroform is added, and the process is repeated. Ether, on the other hand, is lighter than water, and hence if ether had been used it would be necessary to draw off and save the water layer, pour the ether layer into a receiver, pour the water layer back into the separatory funnel, add ether, shake, and repeat the process. The twelve quickly-made chloroform extracts were combined, dried by brief contact with anhydrous sodium sulfate, and the solvent was removed by distillation. The reaction product was a colorless oil which soon solidified, and on crystallization from a mixture of benzene and hexane it afforded shiny plates of pure *cis*-cyclohexane-1,2-diol, m.p. 97–98°.

Outcome of the oxidation

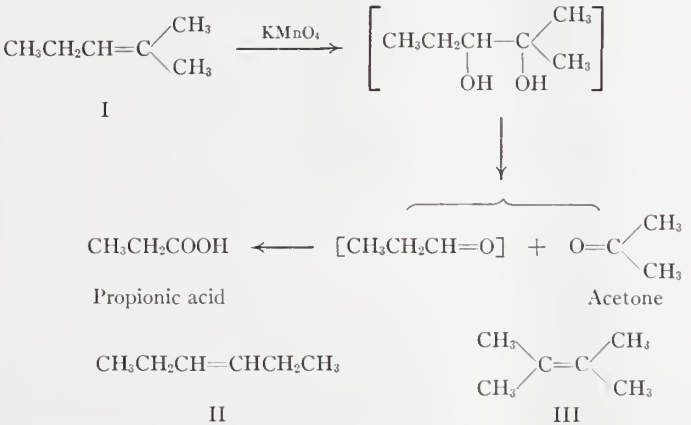


From 16.4 g. of cyclohexene, 7.0 g. of pure *cis*-cyclohexane-1,2-diol is obtained

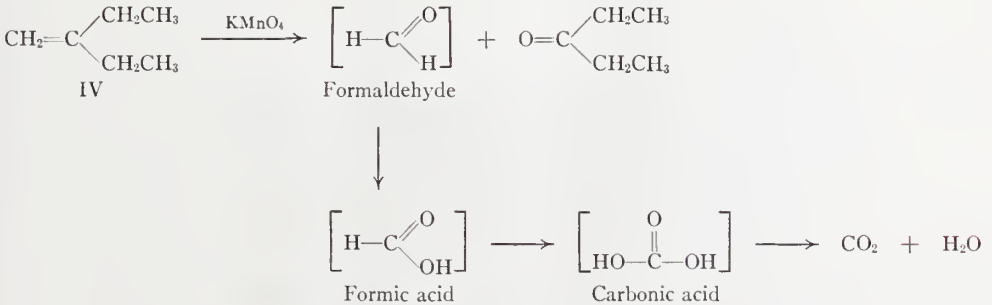
Exhaustive Permanganate Oxidation. — When an alkene is treated in aqueous solution with as much permanganate as can be consumed, the reaction products are either the products of glycol cleavage or their further oxidation products. An aldehyde has an already oxidized carbon carrying a hydrogen atom and this atom is attacked by permanganate and replaced by hydroxyl. The acid is stable to further



oxidation because there is no longer a hydrogen atom to be hydroxylated. A ketone likewise lacks a hydrogen to be hydroxylated and is stable to permanganate. Thus alkene I affords propionic acid and acetone. The alkene II gives two moles of propionic acid, and



III gives two moles of acetone. If an alkene has a terminal double bond, for example IV, the methylene group (CH_2) is converted on glycol cleavage to formaldehyde, which is progressively oxidized by



permanganate to formic acid and then to carbonic acid, which largely decomposes to carbon dioxide and water.

One useful application of exhaustive permanganate oxidation is in establishment of the structures of compounds containing a double

Use in structure determination

bond. Thus the three isomeric alkenes of the formula C_4H_8 are distinguished from one another by the fact that, on exhaustive permanganate oxidation, V gives a three-carbon acid and carbon dioxide and

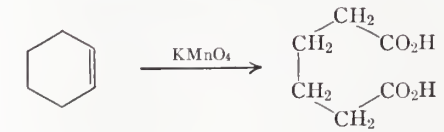
$$\underset{\text{V}}{CH_3CH_2CH{=}CH_2} \longrightarrow CH_3CH_2CO_2H + CO_2$$

$$\underset{\text{VI}}{CH_3CH{=}CHCH_3} \longrightarrow 2\ CH_3CO_2H$$

$$\underset{\text{VII}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2} \longrightarrow CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}O + CO_2$$

therefore has the chain CCC=C, VI gives two moles of a two-carbon acid and is thus CC=CC, and VII gives a three-carbon ketone and carbon dioxide. The reaction also is of preparative value, particularly as applied to readily available cycloalkenes. Thus cyclohexene, on exhaustive permanganate oxidation, affords the dibasic adipic acid.

Preparative use



Cyclohexene — Adipic acid

HYDROGENATION

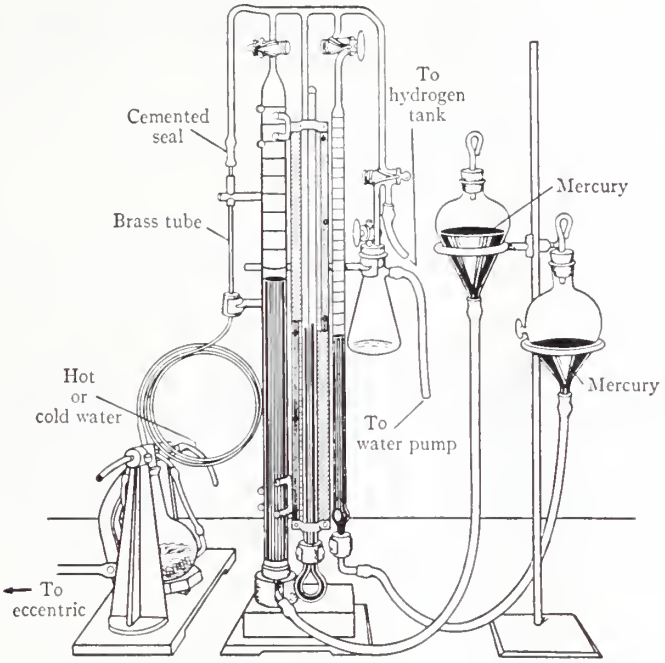
4.23 Unsaturated hydrocarbons, alkenes and alkynes, are able to add hydrogen under the influence of a specific catalyst, or undergo catalytic hydrogenation. Thus an alkene, on catalytic hydrogenation, yields an alkane:



In the absence of a catalyst no reaction occurs. The most potent catalysts are the noble metals platinum and palladium, but, to be effective, these metals must be prepared in the form of extremely fine particles that have a large surface area and are so able to adsorb, or hold onto their surface, both the unsaturated hydrocarbon and hydrogen gas. Roger Adams at the University of Illinois introduced a useful method of preparing active noble-metal catalysts which consists in fusing chloroplatinic acid, H_2PtCl_6, or palladium chloride, $PdCl_2$, with sodium nitrate, digesting the cooled melt with water, and collecting the resulting brown precipitate, which is an oxide of either platinum or palladium. This oxide is suspended in a solvent capable of dissolving the unsaturated hydrocarbon to be hydrogenated,

Noble-metal catalysts

and the suspension is shaken with hydrogen in an apparatus such as that illustrated. The brown oxide is soon converted into a black



Apparatus for Catalytic Hydrogenation at Atmospheric Pressure (Hershberg)

Hydrogen, introduced to the shaker flask through a flexible tube, is taken from either the large or the small burette; the volume of reserve gas present at any time is read on the burette after adjusting the appropriate leveling bulb to a point where the mercury is at the same level in the two arms of the central manometer tube.

suspension of very finely divided platinum or palladium, which is the effective hydrogenation catalyst. The unsaturated compound to be hydrogenated is then introduced and the three-phase system consisting of the solution, the catalyst, and hydrogen gas is shaken until hydrogen is no longer absorbed. Less expensive, but also less active base-metal catalysts (Cr, Ni) can be used by operating at high enough temperatures and pressures to compensate for the lesser activity (Russian-born American chemist Vladimir N. Ipatieff). A widely used copper-chromium oxide catalyst devised by Homer Adkins (University of Wisconsin) is used in an electrically heated hydrogenator of special alloy steel mounted in a mechanical rocker operated at temperatures of 150–250° and pressures of 3000–5000 lbs./sq. in. The American M. Raney described in a patent (1927) a hydrogenation catalyst made by leaching a nickel-aluminum alloy with hot sodium hydroxide solution, which dissolves the aluminum and leaves the nickel as a black, pyrophoric suspension. Raney nickel catalyst is active enough to

Base-metal catalysts

Raney nickel

promote many hydrogenations at room temperature and moderate pressure.

4.24 Catalytic hydrogenation is applicable not only to alkenes but to almost all ethylenic compounds, including unsaturated acids, alcohols, and ketones, as illustrated by the examples. The reaction is thus of

Hydrogenation generally applicable

$$\underset{\text{10-Undecylenic acid (from castor oil)}}{CH_2{=}CH(CH_2)_8COOH} \xrightarrow{H_2\ (Pt)} \underset{\text{Undecylic acid}}{CH_3(CH_2)_9COOH}$$

$$\underset{\text{Geraniol (from rose oil)}}{CH_3C(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCH_2OH} \xrightarrow{H_2\ (Pt)} \underset{\text{Tetrahydrogeraniol}}{CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2OH}$$

general value for the preparation of saturated compounds of various types where suitable unsaturated intermediates are available. It is also of use in investigation of the structure of new compounds, since measurement of the uptake of hydrogen affords a measure of the number of double bonds present. If a hydrocarbon contains x double bonds and the empirical formula is C_nH_m, the number of rings can be calculated from the expression:

Quantitative hydrogenation

$$\text{Number of rings} = n - \frac{m}{2} - x + 1$$

For example, cyclohexene is C_6H_{10} and has one double bond, hence $6 - 5 - 1 + 1 = 1$ ring. Cyclohexadiene is C_6H_8, and the number of rings is $6 - 4 - 2 + 1 = 1$.

4.25 Catalytic hydrogenation is also applicable to both alkynes and carbonyl compounds. It is the only addition reaction common to the following three types of unsaturation:

Hydrogenation of alkynes, aldehydes, ketones

$$\text{C=C} \qquad \text{—C≡C—} \qquad \text{C=O}$$

An alkyne yields first an alkene and then an alkane. Aldehydes and

$$\underset{\text{Alkyne}}{RC{\equiv}CR'} \xrightarrow{H_2\ (Pt)} \underset{\text{Alkene}}{RCH{=}CHR'} \xrightarrow{H_2\ (Pt)} \underset{\text{Alkane}}{RCH_2CH_2R'}$$

$$\underset{\text{Aldehyde}}{RC(H){=}O} \xrightarrow{H_2\ (Pt)} \underset{\text{Primary alcohol}}{RCH_2OH}$$

$$\underset{\text{Ketone}}{R(R')C{=}O} \xrightarrow{H_2\ (Pt)} \underset{\text{Secondary alcohol}}{R(R')CHOH}$$

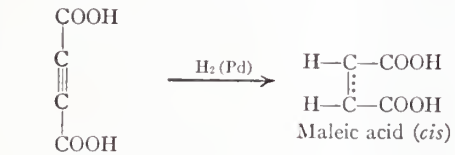
ketones on catalytic hydrogenation yield primary and secondary alcohols, respectively. The fact that carbonyl compounds are hy-

drogenable suggests that, since the positively polarized carbon of the carbonyl group is the point of attack in the characteristically nucleophilic additions of other reagents, hydrogenation is to be classed as a reaction of the nucleophilic type. Such a classification is consistent with the fact that the triple bond is significantly more reactive to hydrogenation than the double bond, as it is in such nucleophilic reactions as addition of hydrogen cyanide. The relationship has useful applications in synthesis, since it permits selective hydrogenation of a triple bond without attack of a double bond. Thus it is possible to hydrogenate an alkyne under conditions so mild that the initially formed alkene is not hydrogenated further. Raney nickel is often used for effecting such selective hydrogenations, and alkenes are obtainable in high yield and purity.

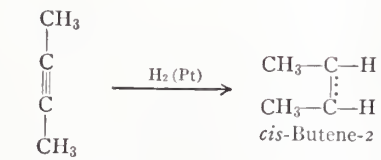
Reactivity: C≡C surpasses C=C

4.26 cis-Addition

A useful feature of catalytic hydrogenation is that it invariably follows the rare course of *cis*-addition. The situation is particularly clear in the case of a disubstituted acetylene where the two possible products are *cis*- and *trans*-isomers. If the conditions are sufficiently mild to prevent isomerization subsequent to reduction, the *cis*-isomer is the sole product. Thus acetylenedicarboxylic acid on hydrogenation



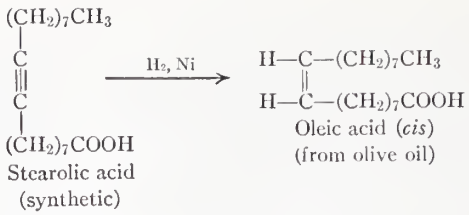
Acetylenedicarboxylic acid — Maleic acid (*cis*)



Butyne-2 — *cis*-Butene-2

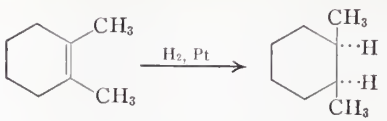
affords maleic acid, in which the two carboxyl groups have been shown to be on the same side of the molecule, and butyne-2 affords *cis*-butene-2. This method of forming compounds with *cis*-double bonds is particularly useful because, since *trans*-compounds are more stable than their *cis*-isomers, other methods usually give *trans*-isomers. Production of an ethylenic compound via an acetylenic compound is a particularly attractive route to the synthesis of unsaturated fatty acids isolated from natural fats because these usually have the less stable *cis*-configuration. For example, oleic acid, the chief acid component from olive oil is a *cis*-compound of the structure formulated. An acid identical with the natural acid has been obtained by selective

Synthetic route to natural (cis) fatty acids



hydrogenation of the corresponding acetylenic acid. Note that the carboxyl group is not hydrogenable.

4.27 Where catalytic hydrogenation of an ethylenic compound can afford isomeric products, the product formed is likewise that resulting from *cis*-addition, as in the example of 1,2-dimethylcyclohexene. Since



all other instances of *cis*-addition are known to follow this course because they proceed through cyclic intermediates, it seems likely that hydrogenation also involves what amounts to a cyclic intermediate. Possibly the substance undergoing hydrogenation lies, on its flattest side, on the hydrogen-saturated catalyst surface, with the unsaturated carbons forming a cyclic complex with the metal. Two hydrogen atoms dissolved in the metal both approach from the under side of the molecule and so give a *cis*-product.

Cyclic intermediate by adsorption on catalyst surface

SUMMARY

Oxidation of ethyl alcohol:

$CH_3CH_2OH \longrightarrow CH_3CH{=}O \longrightarrow CH_3COOH.$

Both steps involve attack at an already oxidized carbon. Second step a hydroxylation of H on an oxidized C; first step interpreted as involving same process: $CH_3CH_2OH \longrightarrow [CH_3CH(OH)_2$, unstable *gem*-diol$] \longrightarrow CH_3CH{=}O$. By same mechanism:

$CH_3OH \longrightarrow CH_2{=}O \longrightarrow HCOOH \longrightarrow CO_2.$

Primary alcohol oxidized (dehydrogenated) to an aldehyde. *sec*-Alcohol ⟶ ketone. *t*-Alcohol (no H on oxidized C) not oxidized. Aldehydes distinguished from ketones by silver mirror test: RCHO is oxidized by silver ammonium ion, and silver separates as a mirror. Test negative for ketones.

Permanganate test positive for (*a*) primary and secondary alcohols, (*b*) aldehydes, and unsaturated hydrocarbons. Types (*a*) distinguished from (*b*) because they react with acetic anhydride to form acetates (esters). Acetylation replaces hydroxylic H by acetate group and hence the acetates give negative permanganate test. *t*-Alcohols are not acetylated because of steric hindrance. A *t*-alcohol and an alkane both negative in the permanganate test, but the former is soluble in concd. H_2SO_4 and the latter is not.

Osmium tetroxide, OsO_4, adds to cyclohexene in ether solution to form a cyclic osmate ester (insoluble) hydrolyzable to *cis*-cyclohexane-1,2-diol. *trans*-Addition the normal course; *cis*-addition occurs when there is a cyclic intermediate which is of necessity *cis*.

Photographic demonstration of the experiment. Quality of sample judged by determination of melting point. Identity established by mixed melting point determination. *trans*-Diols more symmetrical than *cis*-isomers, usually have the higher melting points: example of the two cyclopentane-1,2-diols.

vic-Glycols (adjacent hydroxyls) cleaved by periodic acid: generation of 2 OH radicals, cleavage of weak bond between the oxidized carbons, loss of water from *gem*-diols to form carbonyl compounds.

$$RCH(OH)CH(OH)R \longrightarrow [2\ RCH(OH)_2] \longrightarrow 2\ RCH{=}O.$$

$$R_2C(OH)C(OH)R_2 \longrightarrow [2\ R_2C(OH)_2] \longrightarrow 2\ R_2C{=}O.$$

Cyclic *cis*-glycols cleaved much faster than *trans* (cyclic intermediate probably involved). Cyclohexane-1,2-diols: *cis* cleaved faster than *trans*, but both give adipaldehyde.

Permanganate oxidation of alkenes. Permanganate hydroxylates double bond, effects glycol cleavage, and also oxidizes aldehydes to acids. *vic*-Glycols prepared easily, if in low yield, by oxidation with one oxygen equivalent of reagent at 0°. Products are *cis*-glycols; reaction probably involves a cyclic manganate ester (soluble in water, rapidly hydrolyzed). Photographic demonstration of an oxidation; suction filtration of MnO_2; evaporation; extraction with chloroform ($CHCl_3$ heavier than water); evaporation, and crystallization of product.

Exhaustive permanganate oxidation.

$$RCH{=}CHR \longrightarrow 2\ RCOOH.$$
$$R_2C{=}CR_2 \longrightarrow 2\ R_2CO.$$
$$R_2C{=}CH_2 \longrightarrow R_2C{=}O + CO_2.$$

Use in structure determination: locates position of double bond. Preparative use: oxidation of cyclohexene to adipic acid.

Hydrogenation

Addition of hydrogen to double bond of an alkene in the presence of a hydrogenation catalyst. Adams catalyst: Pt or Pd oxide prepared by fusion of a halide with $NaNO_3$, reduced by H_2 to black, finely divided Pt or Pd; inexpensive base-metal catalysts (Cr, Ni) effective at high temperatures and high pressures (Ipatieff); Adkins Cr-Cu oxide catalyst; Raney nickel catalyst from Al-Ni alloy + NaOH.

Uptake of hydrogen a measure of number of double bonds present. For a hydrocarbon C_nH_m with x double bonds: Number of rings = $n - m/2 - x + 1$.

Other applications of catalytic hydrogenation. Alkyne ⟶ alkene ⟶ alkane. Aldehyde ($RCH{=}O$) ⟶ primary alcohol (RCH_2OH). Ketone ($R_2C{=}O$) ⟶ *sec*-alcohol (R_2CHOH). Hydrogenation of nucleophilic type. Alkynes, more vulnerable than alkenes to nucleophilic attack, are hydrogenated more readily than alkenes. Hence selective hydrogenation of an alkyne to an alkene possible (Raney Ni gives good results).

Hydrogenation follows course of *cis*-addition: acetylenedicarboxylic acid ⟶ maleic acid (*cis*-HOOCCH=CHCOOH). Useful for synthesis of natural unsaturated fatty acids of the less stable *cis*-configuration, e.g. stearolic acid (—C≡C—) ⟶ oleic acid (from olive oil), *cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$. Postulate of a cyclic complex on the catalyst surface.

PROBLEMS

1. One of the four butyl alcohols ($C_4H_{10}O$) gives on oxidation a compound of the formula C_4H_8O, for which the silver mirror test is found to be negative. What is the structure of the alcohol?
2. The formulas of four amyl alcohols are to be derived from that of isopentane,

   $$CH_3CHCH(CH_3)_2,$$

   by systematic replacement of H by OH. One of these alcohols gives a negative permanganate test; which one is it?
3. How would the 2,5-diol

   $$CH_3CH(OH)CH_2CH_2CH(OH)CH_3$$

   respond in the following tests:
   (*a*) Permanganate test
   (*b*) Permanganate test after acetylation
   (*c*) Reaction with periodic acid
4. How could you distinguish between the following isomers:

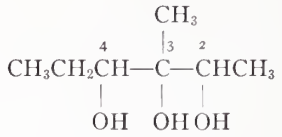
   $$CH_3CHCH_2CH_2CH_2CH_2CH_2OH$$
   $$\quad\ |$$
   $$\quad OH$$
   (*a*)

   $$CH_3CHCH_2CH_2CH_2CHCH_3$$
   $$\quad\ |\qquad\qquad\ |$$
   $$\quad OH\qquad\quad OH$$
   (*b*)

5. How distinguish between the isomers:

   $$CH_3CH_2CHCHCH_2CH_3 \qquad CH_3CH_2CHCH_2CHCH_3$$
   $$\quad\ |\ |\qquad\qquad\qquad\ |\qquad\ |$$
   $$\quad OHOH\qquad\qquad\quad OH\quad OH$$
   (*a*)\qquad\qquad\qquad\qquad (*b*)

6. Suppose that, by controlled partial acetylation, two isomeric monoacetates could be obtained from the triol:



What are the possible formulas of the monoacetates, and how could you distinguish between them?

7. From equation 2 in paragraph 4.17 and the weights of reagents used in the permanganate oxidation photographed (4.18), calculate the amount of permanganate theoretically required and see if excess reagent was used. Calculate the theoretical yield, and the percentage yield actually obtained.
8. How could the following isomers be distinguished:

$CH_3CH{=}CHCH_2COOH$ (*a*) $CH_2{=}CHCH_2CH_2COOH$ (*b*)

9. What products would you expect to arise on exhaustive permanganate oxidation of (*a*) 10-undecylenic acid and of (*b*) geraniol (paragraph 4.24)?
10. A hydrocarbon of the formula $C_{14}H_{20}$ on catalytic hydrogenation absorbs two moles of hydrogen. How many rings does it contain?
11. A pure hydrocarbon of the formula C_6H_{12} decolorizes bromine solution, dissolves in concentrated sulfuric acid, yields *n*-hexane on hydrogenation, and on oxidation with excess potassium permanganate affords a mixture of two acids of the type RCOOH. What is the structure?
12. A hydrocarbon $C_{11}H_{20}$, which on catalytic hydrogenation absorbs two moles of hydrogen, gives on oxidation the products

$CH_3CH_2COCH_3$, $HOOCCH_2CH_2COOH$, and CH_3CH_2COOH. What is its structure?

13. What products would you expect to result from exhaustive catalytic hydrogenation of:
(*a*) $(CH_3)_2C{=}CHCH_2CH_2CH{=}O$
(*b*) $CH_3CH(OH)CH_2CH{=}CHCOOH$
14. Predict the product of selective hydrogenation (one mole of H_2) of:
(*a*) $CH_3CH{=}CHCH_2C{\equiv}CCH_3$
(*b*) The product of addition of acetylene to cyclohexanone (see 3.25).

CHAPTER 5

CONJUGATED DIENES

5.1

Hydrocarbons having two double bonds separated by one or more saturated carbon atoms present no novel features and behave as expected from analogy with monounsaturated alkenes. The hydrocarbons (1) and (2) have identical double bonds at the ends of the

$CH_2{=}CHCH_2CH{=}CH_2$ (1) Pentadiene-1,4 $CH_2{=}CHCH_2CH_2CH{=}CH_2$ (2) Hexadiene-1,5

Isolated double bonds

carbon chains, and these absorb bromine, hydrogen bromide, and hydrogen (in the presence of a catalyst) at the same rate and in the manner expected from the behavior of the monounsaturated analog propylene, $CH_3CH{=}CH_2$. The two double bonds thus function independently of each other and are described as isolated double bonds.

5.2

A different situation is encountered in butadiene-1,3, a hydrocarbon usually referred to as butadiene and available as a petrochemical by dehydrogenation of the mixture of butene-1 and butene-2 produced by cracking. Butadiene has a pair of double bonds adjacent

$$\underset{\text{Butene-1}}{CH_3CH_2CH{=}CH_2} \xrightarrow{-\,2H} \underset{\text{Butadiene}}{CH_2{=}\overset{3}{C}HCH{=}\overset{1}{C}H_2} \xleftarrow{-\,2H} \underset{\text{Butene-2}}{CH_3CH{=}CHCH_3}$$

to each other. It is known as a conjugated diene, and the system C=C—C=C is described as a conjugated system. The significance of the term is that when a conjugated diene participates in an addition reaction the two centers of unsaturation function as a unit rather than as isolated double bonds.

Conjugated diene

5.3

When butadiene is treated with bromine, the first molecular equivalent of reagent is taken up so much more rapidly than the second that a dibromide fraction is easily isolated. The 1,2-dibromide is a minor component of this fraction; the principal component carries bromine

$$CH_2{=}CHCH{=}CH_2 \xrightarrow{Br_2} \underset{\text{1,4-addition (major product)}}{BrCH_2CH{=}CHCH_2Br} + \underset{\text{1,2-addition (minor product)}}{CH_2{=}CHCHBrCH_2Br}$$

1,4-Addition

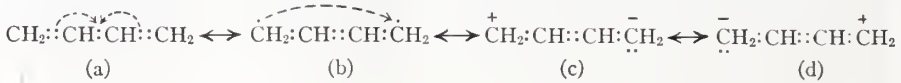
atoms not on adjacent carbon atoms but at the terminal positions 1 and 4. The main reaction is thus a 1,4-addition to the conjugated system and involves disappearance of both original double bonds with establishment of a new double bond at the 2,3-position.

5.4 The special mode of addition of butadiene is associated with special characteristics of the molecule disclosed by physical measurements. Thermochemical data show that butadiene is significantly more stable, in the sense of having a lower energy content, than dienes with isolated (nonconjugated) double bonds; and electron-diffraction measurements reveal abnormality in bond length, defined as the distance between atomic centers. The normal bond length for the C—C link is 1.54 Å and for the isolated C=C link the distance is 1.34 Å. In butadiene the central bond in the molecule, represented in the ordinary formula as a single link, actually has a bond distance of 1.46 Å, intermediate between a double and a single bond; the two terminal bonds are somewhat longer than an isolated double bond. The evidence suggests that the three bonds linking the carbon atoms are neither true double nor true single bonds but something of an intermediate character.

Bond shortening

5.5 The resonance theory accounts for the facts cited on the postulate of certain redistributions of electrons. Thus redistribution of the

Redistribution of electrons



electrons in formula (a) in the directions indicated by the dotted lines (one electron of each double bond moved to the center) would give structure (b), which has a central double bond, two terminal single bonds, and terminal carbon atoms each having an unpaired electron. An electron transfer in (b) from one terminal carbon atom to the other could give a polarized species, (c) or (d), depending upon the direction of transfer. These four structures differ merely in the positions of the electrons. According to the resonance theory, when a substance can have two or more equivalent or nearly equivalent structures, the actual molecule does not conform to any one of the structures but exists as a resonance hybrid of the principal contributing structures.

5.6 The diradical (b) is probably a very minor contributor, and hence butadiene can be regarded as a resonance hybrid of (a), (c), and (d). The equivalent Kekulé formulation is:

$$\underset{(a')}{CH_2{=}CH{-}CH{=}CH_2} \longleftrightarrow \underset{(c')}{\overset{+}{C}H_2{-}CH{=}CH{-}\overset{-}{C}H_2} \longleftrightarrow \underset{(d')}{CH_2{-}CH{=}CH{-}\overset{+}{C}H_2}$$

Resonance

The resonance concept explains why the central linkage partakes of the character of both a single and a double bond. Bond shortening is a necessary consequence of such a resonance effect, as is the lengthening of the terminal linkages in consequence of their partial single-bond character.

A further consequence of resonance is dissipation of energy, or thermodynamic stabilization. Conversely, thermodynamic data afford a measure of the magnitude of resonance stabilization. The average heat of hydrogenation of propylene, butene-1, and other alkenes having the terminal-bond structure of butadiene is 30.3 kg.-cal./mole. The heats of hydrogenation of the nonconjugated pentadiene-1,4 and hexadiene-1,5, namely 60.8 and 60.5 kg.-cal./mole, are almost twice this value. The value observed for butadiene, however, is only 57.1 kg.-cal./mole, and hence this hydrocarbon has a lower energy content than that corresponding to two isolated double bonds. The difference of 3.5 kg.-cal./mole represents the resonance stabilization, or resonance energy, of butadiene.

5.7

Resonance energy

Any structure contributing to a resonance hybrid may participate in a reaction such as bromination. If structure (a′) of butadiene is attacked by Br^+, the resulting carbonium ion would be a resonant hybrid of structures (e′) and (f′); attack of the polarized structure (c′) would afford the same hybrid ion. The combination of this hybrid with bromide ion can give either the 1,2- or the 1,4-addition product; the preponderance of the 1,4-product suggests that structure (f′) is the major contributor or the more reactive species of the carbonium ion hybrid.

5.8

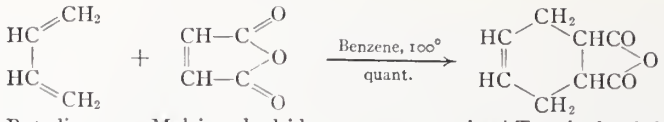
$$\left.\begin{array}{c} CH_2{=}CHCH{=}CH_2 \\ (a') \\ \updownarrow \\ \overset{+}{C}H_2CH{=}CH\overset{-}{C}H_2 \\ (c') \end{array}\right\} \xrightarrow{Br^+} \left\{\begin{array}{c} CH_2{=}CH{-}\overset{+}{C}HCH_2Br \\ (e') \\ \updownarrow \\ \overset{+}{C}H_2{-}CH{=}CHCH_2Br \\ (f') \end{array}\right. \xrightarrow{Br^-} \left\{\begin{array}{l} CH_2{=}CHCHBrCH_2Br \\ (1,2\text{-product}) \\ \\ BrCH_2CH{=}CHCH_2Br \\ (1,4\text{-product}) \end{array}\right.$$

Explanation of 1,4-addition

Diels-Alder Reaction. — This widely applicable synthetic reaction was discovered in Germany in 1928 by Professor Otto Diels and his student Kurt Alder; the important contribution was recognized by the joint award to the discoverers, of the Nobel Prize in chemistry for 1950. The reaction is between a conjugated diene and a second component, a dienophile, of the type represented by maleic anhydride. When the reactants are mixed and heated, butadiene undergoes 1,4-addition with formation of a new double bond at the 2,3-position,

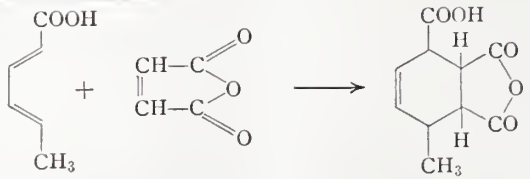
5.9

Diene and dienophile



Butadiene + Maleic anhydride → *cis*-Δ^4-Tetrahydrophthalic anhydride (m.p. 104°)

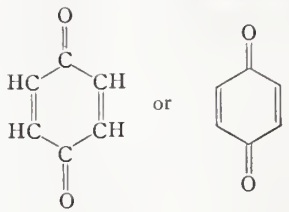
and the terminal carbon atoms become attached to the unsaturated carbon atoms of the anhydride to form a six-membered ring. The yield in the reaction cited is very high, and the same is true for many Diels-Alder reactions. Dienes of a variety of types react similarly. For example, sorbic acid, a substance isolated from unripe berries of the mountain ash (*Sorbus*), adds to maleic anhydride to form a typical Diels-Alder adduct.



Sorbic acid

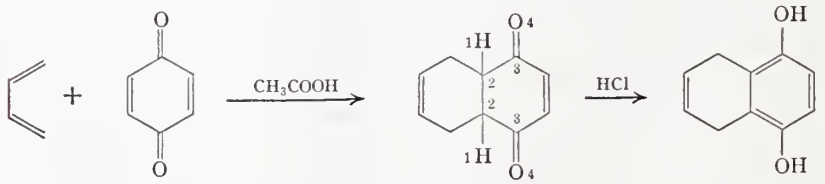
5.10 Maleic anhydride, a typical dienophilic Diels-Alder reactant, has a carbon–carbon double bond flanked by two carbonyl groups and thus contains the conjugated system: O=C—C=C—C=O. Certain other compounds having carbonyl groups conjugated with a carbon–carbon double bond also function as Diels-Alder dienophiles. One is quinone, a yellow substance of extraordinarily high reactivity to a

Quinone as dienophile



Quinone

variety of reagents. It adds butadiene in acetic acid to form an adduct which is easily isomerized by a mineral acid catalyst to the dihydronaphthohydroquinone formulated.

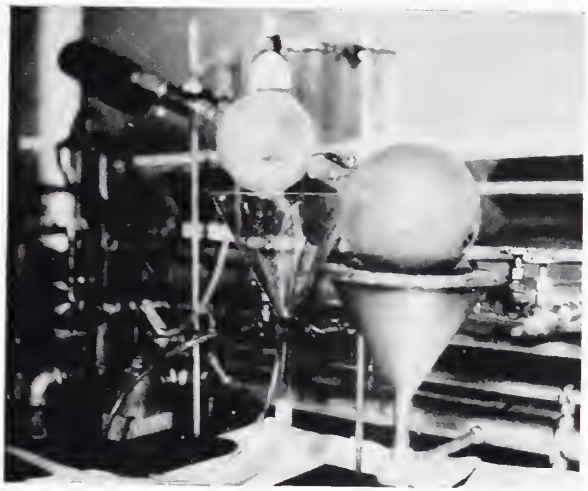


Butadiene Quinone Adduct Dihydronaphtho-hydroquinone

The Diels-Alder reaction of quinone with butadiene is conducted as follows. Commercial quinone, usually a dull yellow solid, is purified by steam distillation, an operation conveniently carried out in vacuum in a rotating evaporator as shown in the photograph (see also frontispiece). A charge of crude quinone and water is placed in the large

5.11

Description of an experiment



Steam distillation in a rotating evaporator

flask, which is rotated over the steam bath. This distillation flask is connected by a ground-glass joint to a receiving flask, which is cooled with a shower of water delivered from a transparent Tygon tube through a small plastic Büchner funnel. Vapor passes from the large flask through a tube sealed into the receiving flask and having holes at the upper end. The electric motor rotates both flasks; the rotating shaft has a hollow core connecting the two flasks to the suction pump. In the lower flask, spreading out of the solution in a thin film hastens evaporation and prevents bumping; in the upper receiving flask, the rotary motion facilitates cooling, and hence condensation of the distillate.

5.12

One mole (108 g.) of pure, bright yellow quinone is suspended in 500 ml. of acetic acid in a 1-l. Erlenmeyer flask, and the suspension is cooled in an ice bath until the solvent acetic acid begins to crystallize (m.p. 16.7°). Butadiene gas (b.p. −4°) is run from a steel cylinder into an Erlenmeyer flask cooled in dry ice and bearing a wax-pencil mark to indicate the volume corresponding to 1.1 mole of the diene component. The liquid condensate is collected to the marked point and added to the chilled acetic acid suspension of quinone. The flask is closed with a rubber stopper, which is wired in place to retain the volatile butadiene, and covered with a towel for protection in case the flask should break (a). The flask is then put in a cooling bath



(a)



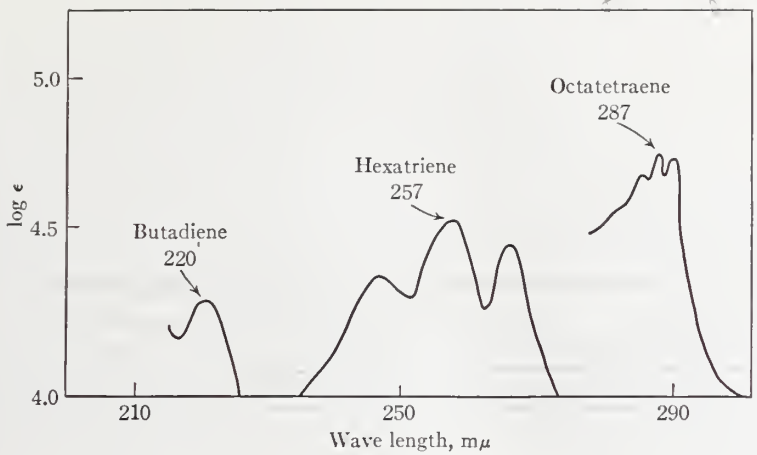
(b)

Stages in the reaction

maintained at a temperature of 10–15°, and occasionally swirled. In 40–48 hours the crystals and yellow color of quinone have disappeared, and a nearly colorless solution of the adduct results. A hot solution of concentrated hydrochloric acid (100 ml.) in water (500 ml.) is added to effect isomerization and the solution heated on the steam bath. Colorless crystals of dihydronaphthohydroquinone soon begin to separate (b); the yield is 143 g. (88%).

5.13 **Light Absorption.** — Butadiene is colorless, which means that it does not absorb light in the visible region of the spectrum, a region of wave length in the range 400–700 mμ (millimicrons). The hydrocarbon does, however, absorb ultraviolet light over a specific, narrow range of wave length. Compounds having isolated double bonds absorb ultraviolet light, but in the region below 200 mμ, not ordinarily measurable with standard instruments. Butadiene absorbs ultraviolet light of wave length above 200 mμ, and this property is a useful identifying characteristic. The phenomenon is due to transition of electrons from one orbital to another. In the absence of light, electrons of the molecule travel in orbitals of the lowest possible energy, a condition described as the ground state. On irradiation with ultraviolet light, specific light waves are destroyed in causing transition of appropriate electrons of butadiene from the ground state to orbitals of higher energy level. Hence a part of the light passing through a dilute solution of butadiene is not transmitted but is absorbed. The absorption is over a narrow range, about 215 to 225 mμ, and is at a maximum of intensity at 220 mμ. Thus butadiene is described as having an ultraviolet absorption maximum at a wave length of 220 mμ, or $\lambda_{max} = 220$ mμ. The absorption spectrum is shown in the

Absorption of ultraviolet light



Ultraviolet absorption spectra

chart, in which wave length is plotted against intensity of absorption, expressed as the logarithm of the extinction coefficient (ϵ).

Other conjugated dienes likewise show selective ultraviolet absorption and are thereby distinguishable from nonconjugated dienes. The wave length of absorption is influenced to a minor extent by structural changes. Thus, in dienes such as those listed below, the absorption band is shifted about 5 mμ to longer wave length for each alkyl group joined to the diene system: 5.14

		λ_{max}, mμ
Piperylene	$CH_3CH{=}CHCH{=}CH_2$	224
2,3-Dimethylbutadiene-1,3	$CH_2{=}C(CH_3){-}C(CH_3){=}CH_2$	230
1,1,4,4-Tetramethylbutadiene-1,3	$(CH_3)_2C{=}CHCH{=}C(CH_3)_2$	240

Effect of alkyl substituents

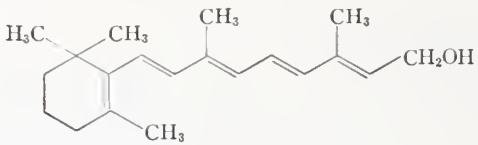
Extension of the conjugated system shifts the absorption band in the direction of longer wave length, and also increases intensity of absorption. Both relationships are evident from the graph and from the following summary:

	λ_{max}	log ϵ
$CH_2{=}CHCH{=}CH_2$ Butadiene	220	4.32
$CH_2{=}CHCH{=}CHCH{=}CH_2$ Hexatriene-1,3,5	257	4.54
$CH_2{=}CHCH{=}CHCH{=}CHCH{=}CH_2$ Octatetraene-1,3,5,7	287	4.72

Effect of further conjugated double bonds

By making spectrographic determinations at very high dilution, the absorption bands of the triene and tetraene are seen to be resolvable into three separate bands, whereas the low-intensity band of butadiene shows no comparable fine structure. The next member of the series

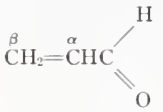
Absorbs visible light, is yellow



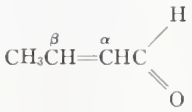
Vitamin A

is not known, but vitamin A has been characterized as having a system of five conjugated double bonds. It not only absorbs ultraviolet light, with λ_{max} 326 mμ, but also absorbs in the visible region of the spectrum and is a crystalline yellow substance.

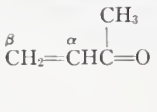
5.15 Carbonyl compounds having an ethylenic bond conjugated with the carbonyl group are stabilized by resonance and also absorb ultra-



Acrolein



Crotonaldehyde



Methyl vinyl ketone

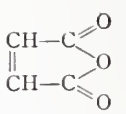
Conjugated α,β-unsaturated aldehydes and ketones

violet light. Thus acrolein and crotonaldehyde have an absorption maximum comparable to that of butadiene; they are described as α,β-unsaturated aldehydes. Methyl vinyl ketone, an α,β-unsaturated ketone, also absorbs in the ultraviolet. Methyl allyl ketone, a non-

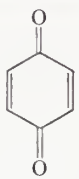


Methyl allyl ketone

conjugated β,γ-unsaturated ketone, does not show comparable absorption. The two Diels-Alder dienophiles discussed above, maleic anhydride (5.9) and quinone (5.10), contain conjugated systems and



Maleic anhydride
λ_{max} 210 mμ



Quinone
λ_{max} 242 mμ

both exhibit selective absorption of light. Maleic anhydride has an ethylenic group conjugated at each end with a carbonyl group. Quinone has a more elaborate conjugated system in which each of two ethylenic groups is conjugated with two carbonyl groups, and it absorbs light not only in the ultraviolet but in the visible region of the spectrum and is bright yellow. Some of the most important dyes owe their color to the presence of a quinone or a quinonoid group.

Absorption producing color

SUMMARY

Isolated double bonds, separated by one or more saturated carbon atoms, function independently. Butadiene (by cracking of butene-1 and butene-2) a conjugated diene, $CH_2{=}CHCH{=}CH_2$. The two double bonds function as a unit.

1,4-Addition of bromine. Energy content lower than for a nonconjugated diene. Bond distances abnormal.

Resonance. Chief contributing structures:

$$CH_2{=}CH{-}CH{=}CH_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}\overset{-}{C}H_2$$
$$\longleftrightarrow \overset{-}{C}H_2{-}CH{=}CH{-}\overset{+}{C}H_2.$$

Butadiene a hybrid of these structures. Accounts for lengthening of the 1,2- and 3,4-bonds and shortening of the 2,3-bond.

Resonance energy of butadiene: 3.5 kg.-cal. Difference in actual heat of hydrogenation and that calculated for a nonconjugated diene.

Interpretation of 1,4-addition: involves ionic resonance structures.

Diels-Alder reaction: 1,4-addition of butadiene to maleic anhydride (dienophile) to produce a cyclohexene derivative. Other conjugated dienes add, e.g. sorbic acid ($CH_3CH{=}CHCH{=}CHCOOH$). Quinone (yellow) another dienophile. Photographs of purification and reaction with butadiene.

Butadiene absorbs ultraviolet light. Absorption maximum at wave length of 220 mμ (millimicrons), or λ_{max} = 220 mμ. Absorption shifted to longer λ by each alkyl substituent (5 mμ) and by each double bond extending the conjugation (about 30 mμ).

α,β-Unsaturated aldehydes and ketones have a conjugated system, C=C—C=O, and likewise show ultraviolet absorption. Conjugated system of maleic anhydride responsible for light absorption. Quinone, with a more elaborate system, absorbs both in the ultraviolet and in the visible (is bright yellow).

PROBLEMS

1. Addition products are formed in good yield from each of the following pairs of reactants. Write equations for the reactions.
   (*a*) Piperylene ($CH_3CH{=}CHCH{=}CH_2$) and maleic anhydride.
   (*b*) 2,3-Dimethylbutadiene-1,3 and crotonic acid, $CH_3CH{=}CHCO_2H$.
   (*c*) Butadiene and diethyl acetylenedicarboxylate, $C_2H_5OOCC{\equiv}CCOOC_2H_5$.
2. Write the formula for cyclopentadiene-1,3. Would you expect this hydrocarbon (*a*) to show ultraviolet absorption in the measurable region, and (*b*) to add to maleic anhydride?
3. A hydrocarbon, C_7H_{10}, shows ultraviolet absorption and on drastic permanganate oxidation gives the products:

$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3 \quad + \quad HOOC{-}COOH$$

   What is its structure?
4. A hydrocarbon of the formula C_6H_8 shows no absorption in the ultraviolet and on catalytic hydrogenation absorbs two moles of hydrogen and gives cyclohexane. What is its structure?
5. Would you expect hexatriene-1,3,5 to react with one mole of bromine to give the 1,6-addition product?

CHAPTER 6

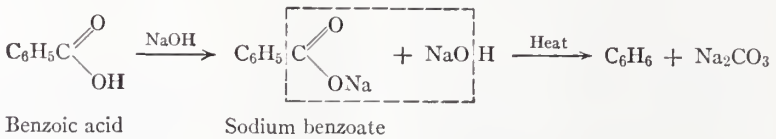
AROMATIC HYDROCARBONS

6.1 **Structure and Source of Benzene.** — Benzene, a highly flammable liquid of penetrating odor, has the molecular weight 78 and the boiling point 80° and is therefore unassociated in the liquid state.

Discovery of benzene

The hydrocarbon was discovered in England in 1825 by Michael Faraday, who isolated the substance from an oily condensate deposited from compressed coal gas. In 1834 the German Eilhard A. Mitscherlich obtained an identical hydrocarbon by fusing benzoic acid with alkali. The reaction involves decomposition of sodium benzoate to

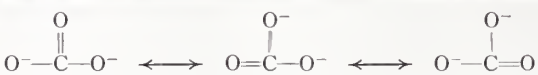
By decarboxylation of benzoic acid



Benzoic acid Sodium benzoate

sodium carbonate, which is the more stable salt of the two because three resonance structures contribute to the hybrid carbonate ion:

Resonant carbonate ion



The overall result is decarboxylation of the acid: $C_6H_5COOH \longrightarrow C_6H_6 + CO_2$. Benzoic acid was so named because it had been discovered as a constituent of the balsamic resin gum benzoin, and the hydrocarbon derived from it by decarboxylation was given the name benzene.

Name

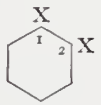
6.2 A few other natural products were also degraded to benzene in the same period, and so recognized as belonging to the aromatic series, but the substance remained a rarity until a practical source was discovered by A. W. von Hofmann in 1845. Hofmann, at the age of 27, had just left Germany on invitation of German-born Prince Albert of England to become the first organic chemist to teach and conduct

From coal tar

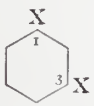
research in England. He found that benzene can be obtained in abundant quantity by redistillation of coal tar, a by-product of the conversion of coal into coke for use in metallurgy. Coal tar was subsequently found to contain an array of other aromatic hydrocarbons, and hence a new set of starting chemicals was available if uses for them could be found. In 1856 W. H. Perkin, a young English student of Hofmann, discovered a way of transforming hydrocarbons from coal tar into a dye which he named mauveine. Mauveine, the first synthetic dye to be introduced and the first rival of the natural dyes indigo and alizarin, soon acquired great popularity and stimulated extensive investigation of coal tar products and widespread search for routes to other dyes, some of which were successful. Indeed the discovery of mauveine initiated development of what has now become a dominant factor in world economics: the synthetic organic chemical industry. Perkin's initial discovery was the result of fortunate circumstance coupled with industry and vision. Subsequent spectacular advances based on empirical findings continued for a time, but the young industry could hardly have enjoyed normal growth for long without elucidation of the chemical nature of benzene. The Kekulé theory of valence announced in 1859 accounted for most known compounds of the methane series but did not at first appear applicable to benzene, since the formula C_6H_6 indicates a highly unsaturated molecule and yet benzene behaves more like a saturated compound. Thus the hydrocarbon is not oxidized by permanganate and does not decolorize bromine solution in the usual test for unsaturation.

6.3 Deduction from number of substitution products

In 1865 it occurred to Kekulé that the structure of the hydrocarbon should be deducible from the number of its substitution products, just as the structure of propane follows from the fact that this hydrocarbon affords two mono-, four di-, and five trichloro derivatives. From an evaluation of the still fragmentary and partly



ortho
1,2



meta
1,3

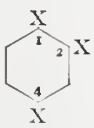


para
1,4

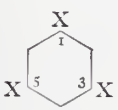
Di- and tri-substitution products



1,2,3



1,2,4



1,3,5

erroneous data on hand, Kekulé concluded that benzene must have a structure allowing for only a single product of monosubstitution and for three disubstitution products, and saw that these relationships can be accounted for only on the basis of a cyclic formula. A ring of six carbon atoms, each carrying a hydrogen atom, would explain the equivalence of all six possible positions for monosubstitution and account for the existence of three di derivatives. The possibilities for di- and trisubstitution are shown with outline formulas. As new compounds were prepared and characterized and old ones reinvestigated, abundant evidence soon accumulated that left no doubt of the correctness of this part of Kekulé's theory, for the number of isomers in different series invariably corresponded with the predicted number.



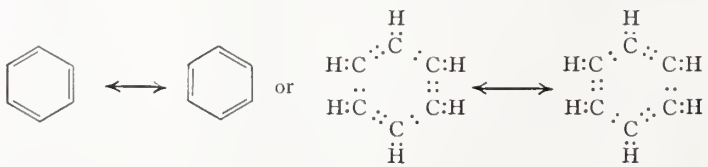
August Kekulé,
1829–96
Born at Darmstadt, Germany; professor at the University of Bonn

6.4

Inert character

To dispose of the remaining carbon valences, Kekulé proposed for benzene the formula of cyclohexatriene, (a) or (b), but the formula was contested for many years because chemists of the period could not reconcile a formula containing three double bonds with the fact that benzene is peculiarly inert in comparison with alkenes and is

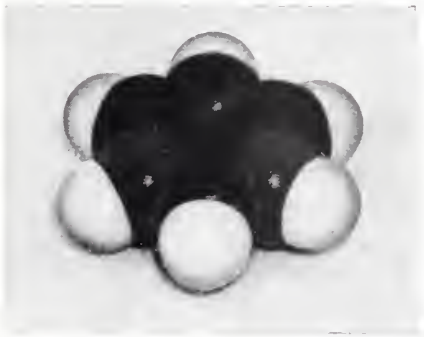
A resonant hybrid



(a) (b) (c) (d)

indifferent to many oxidizing and addition-type reagents to which alkenes are responsive. However, the resonance theory provides a simple explanation. The two Kekulé forms (a) and (b), or the electronic counterparts (c) and (d), are identical resonance structures which contribute equally to the resonant hybrid. X-ray analysis has shown that the six carbon and six hydrogen atoms all lie in a plane and that the six carbon–carbon bonds all have the identical length 1.40 Å, which is shorter than the average value of 1.46 Å for three nonresonant double and three single bonds. The Stuart model

Bond length



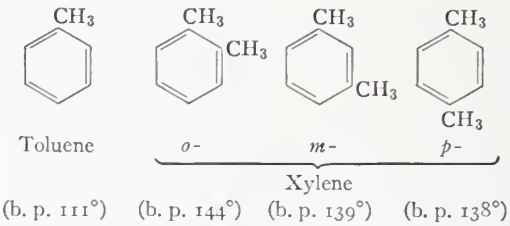
Stuart model of benzene

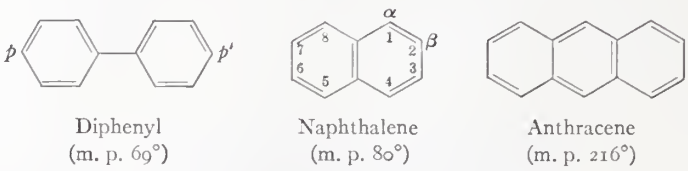
shows the shape of the molecule. Unlike the case of butadiene, redistribution of electrons in the hybrid does not even require partial bond polarization. Resonance stabilization is much greater in the symmetrical cyclic system, and the resonance energy amounts to 36 kg.-cal., as compared to 3.5 kg.-cal. for butadiene. Thus resonance accounts for the stable, inert character often described as aromaticity. A phenyl group, C_6H_5—, is so inert in comparison with alkenes that allylbenzene, $C_6H_5CH_2CH{=}CH_2$, can be put through reactions such as bromine addition to the double bond, oxidation to $C_6H_5CH_2CO_2H$, or hydrogenation to $C_6H_5CH_2CH_2CH_3$ without alteration of the phenyl group.

Phenyl group

Other Coal Tar Hydrocarbons. — Toluene, another constituent of coal tar, boils 21° higher than benzene, and the two are separable by fractional distillation. The three xylenes are produced more abundantly from petroleum (8.19) than from coal tar. Diphenyl consists of two phenyl groups joined by a single bond; the derivative with methyl groups in the two *para* positions is called *p,p'*-dimethyldiphenyl. Naphthalene has two benzene rings fused together in the *ortho* positions; monosubstitution products are designated α- or β-, and polysubstitution products are identified by numbers. Anthracene has three benzene rings fused in a linear manner; the angular isomer is phenanthrene. Coal tar also contains heterocyclic analogs of the

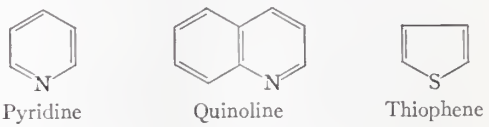
6.5





hydrocarbons. Thus a basic fraction extracted by acid contains pyridine and quinoline, analogs of benzene and of naphthalene, re-

Heterocyclic aromatics



spectively. Benzene boils at 80°, and its sulfur analog thiophene, which is present in coal tar in small amounts, boils at 84°. Thus coal-tar benzene, unless specially processed, contains a trace of thiophene. The resemblance to benzene is so marked that the presence of the substance in coal-tar benzene remained unsuspected till an incident in one of Victor Meyer's lectures at Heidelberg provided a clue leading to the discovery of the sulfur heterocycle (1882). Meyer periodically demonstrated to his students a supposedly characteristic color test for benzene, which consists in shaking a sample with concentrated sulfuric acid and a crystal of isatin, but on one occasion he applied the test in expectation of proving that benzoic acid on decarboxylation gives benzene. The beautiful blue color failed to appear, since the color reaction is specific for thiophene and not for benzene.

AROMATIC SUBSTITUTIONS

6.6 In the absence of light and catalysts, bromine does not attack benzene. However, when ferric bromide is added as catalyst and mild heat is applied, reaction occurs with liberation of hydrogen bromide and formation of bromobenzene. The reaction is a substitution,



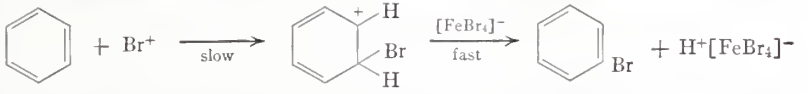
Bromobenzene

rather than an addition, as in the case of an alkene. The difference will be seen to be a consequence of the resonance stabilization of the aromatic ring. Actually, the initial step is the same in each case, namely electrophilic attack by Br^+. Ferric bromide is an efficient catalyst because it combines with bromine as in (a) to form an ionic complex with a strongly developed electrophilic part. After Br^+

(a) $Br_2 + FeBr_3 \longrightarrow Br^+[FeBr_4]^-$

(b) $H^+ + [FeBr_4]^- \longrightarrow H^+[FeBr_4]^-$

has attacked benzene, the anion of the complex functions as acceptor for hydrogen ion (b). Thus the mechanism of bromine substitution (1) involves electrophilic attack to form an intermediate carbonium ion,

1. 

Mechanism of halogenation

which then eliminates H^+ with restoration of the aromatic ring. The carbonium ion does not combine with Br^- to give a dibromide, as the corresponding carbonium ion from an alkene does, because the dibromide would lack the powerful resonance stabilization of the aromatic ring of bromobenzene. If a proton acceptor is available, the driving force favors exclusive formation of the substitution product. Reaction-rate studies have shown that the first step of the reaction is slower than the second step and thus controls the overall rate of the reaction. In other words, the carbonium ion expels a proton faster than the ion is formed.

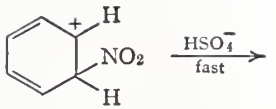
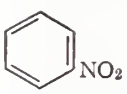
6.7

Nitration follows same course

Another generally applicable aromatic substitution is nitration, exemplified by the conversion of benzene into nitrobenzene: $C_6H_6 + HONO_2 \longrightarrow C_6H_5NO_2 + H_2O$. Nitration has been shown (Ingold, Hughes) to involve the electrophilic nitronium ion, NO_2^+, and the reaction is usually conducted in sulfuric acid solution because this acid promotes formation of the required electrophile by reaction (c).

(c) $HNO_3 + 2\,H_2SO_4 \longrightarrow NO_2^+ + H_3O^+ + 2\,HSO_4^-$

In the terminal step of the nitration, the ion HSO_4^- serves as proton acceptor. Nitration thus follows a two-step course (2) analogous to bromination. The intensity of nitration can be regulated to meet

2. $C_6H_6 \xrightarrow[\text{slow}]{NO_2^+}$  $\xrightarrow[\text{fast}]{HSO_4^-}$  $+ H_2SO_4$

Attack by NO_2^+

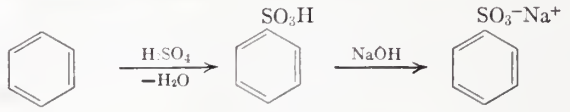
specific requirements of aromatic reactants. If the compound is very reactive, dilute nitric acid is used; if more drastic conditions are required, use can be made of concentrated acid (71%) or fuming acid

(90%), or mixtures of nitric and sulfuric acids. Further control over the reaction is possible by adjustment of the temperature. Thus a given nitration can be described as proceeding very easily, readily, or with difficulty, according to the conditions required for effecting reaction.

6.8

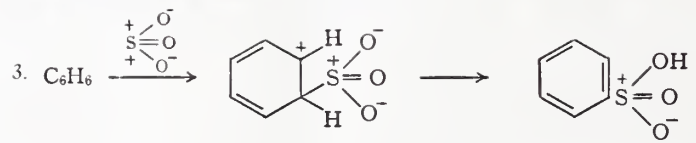
Sulfonation

Another substitution, sulfonation, is carried out by heating an aromatic hydrocarbon with concentrated or fuming sulfuric acid at an appropriate temperature. Benzenesulfonic acid, the product from



Benzenesulfonic acid — Sodium benzenesulfonate

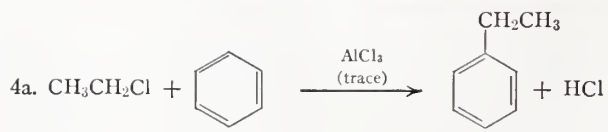
benzene, is a hygroscopic, strong acid and it is usually converted to the neutral, crystalline sodium salt. Sodium sulfonates are readily soluble in water, and water-insoluble hydrocarbons are often sulfonated to produce water-soluble derivatives. Studies of the sulfonation reaction indicate that sulfur trioxide is the reactive electrophile and that the reaction is analogous to bromination and nitration (3).



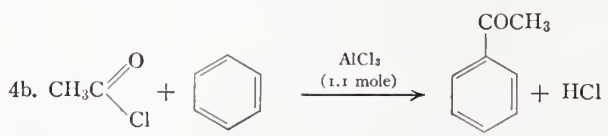
6.9

A fourth substitution, analogous to the other three, is called the Friedel-Crafts reaction; the discoverers (1877) were Charles Friedel, professor in Paris, and his American student James M. Crafts. In one type of Friedel-Crafts reaction (4a) an alkyl chloride reacts with benzene in the presence of a catalytic amount of anhydrous aluminum chloride to give an alkylbenzene. Still more useful is the Friedel-Crafts ketone synthesis (4b), in which the same catalyst promotes

Friedel-Crafts alkylation and acylation



Ethylbenzene



Acetophenone

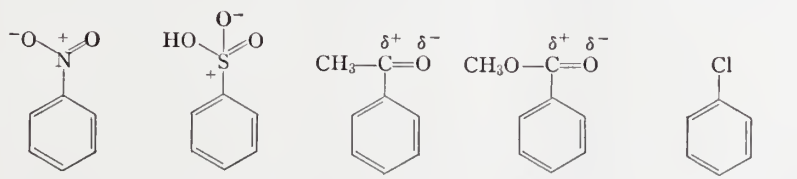
reaction of an aromatic hydrocarbon with an acid chloride to produce a keto derivative such as acetophenone. In the latter reaction a little over one mole of aluminum chloride is required because the reagent is bound by the carbonyl group of the acid chloride to form a complex. An acid anhydride serves as satisfactorily as an acid chloride. Benzoyl chloride, C_6H_5COCl, can also be used. Alkylation (4a) involves attack of the benzene ring by the positive, electrophilic ion of the complex formed by the alkyl halide with the catalyst, $R^+AlCl_4^-$. Acylation (4b) involves similar functioning of the complex $RC^+{=}O[AlCl_4]^-$.

Effect of Groups on Ease of Substitution. — A substituent already present in the benzene ring often influences markedly the ease with which any of the four substitution reactions will proceed. Some groups decrease activity, or deactivate the benzene ring for substitution, and other groups have an activating effect and enable substitution to be carried out under conditions milder than those required for substitution of benzene. Thus benzene can be nitrated with a mixture of concentrated nitric and sulfuric acid at 60°, but conversion of nitrobenzene into a dinitrobenzene requires fuming nitric acid and concentrated sulfuric acid at 95°. The nitro group is thus a deactivator. On the other hand, phenol, which is the hydroxy derivative of benzene, can be nitrated with 20% nitric acid at 25°; the hydroxyl group therefore activates the ring for substitution. 6.10

Activation and deactivation

The activating or deactivating influence of a substituent is attributable to an inductive, or electrostatic, effect, which can operate in either of two directions. Since all substitutions in the benzene ring involve initial attack by a positively charged ion, an electrophile, a group in which the key atom attached to the ring is positively charged or positively polarized repels the attacking electrophile and so decreases susceptibility to substitution. A group which does not carry a positive charge but which is electron-attracting also has a deactivating inductive effect. Since the nitro group contains a semipolar bond, the nitrogen atom carries a positive charge and renders the group strongly electron-attracting. Thus the nitro group induces 6.11

Inductive effect



Electron-attracting, deactivating groups

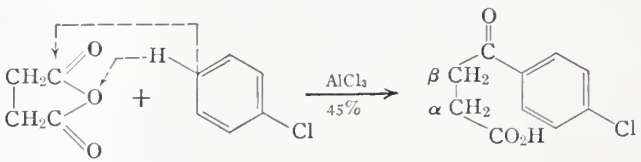
a drift of electrons in its direction and so decreases the electron density at all positions in the ring and makes them less susceptible to attack by Br^+, NO_2^+, etc. The sulfonic acid group has a positively charged key atom attached to the ring and is also strongly deactivating. The carbonyl group of ketones and esters has a partially polarized carbon atom and produces a deactivating inductive effect, which, however, is not so strong as that of the nitro group, as is evident from the relative dipole moments of the groups (given under the formulas). The chlorine atom, which can be seen from the dipole moment to be weakly electron-attracting, has a weak deactivating influence.

6.12

Friedel-Crafts reaction inhibited by a deactivator

In nitrations, sulfonations, and halogenations, a single substituent of one of the above deactivating types merely necessitates use of conditions more forcing than if the substituent were not present. In the case of the Friedel-Crafts reaction, however, a potently electron-attracting group completely inhibits reaction under the most drastic conditions available. Thus nitrobenzene can neither be alkylated with an alkyl chloride and aluminum chloride nor acylated with acetyl chloride or acetic anhydride in combination with the same catalyst. Similarly indifferent to Friedel-Crafts reactions are aromatic ketones, aldehydes, esters, acids. Acetophenone, the product of Friedel-Crafts acylation of benzene, cannot be acylated further, which means that the initial acylation is a sharp stopping point and that

Chlorine a weak deactivator



Succinic anhydride

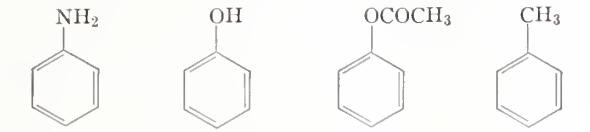
β(*p*-Chlorobenzoyl)-propionic acid

there is thus no danger of the reaction proceeding too far. The weakly deactivating chlorine atom does not stop the Friedel-Crafts reaction but it does lead to lower yields. Thus chlorobenzene can be acylated with succinic anhydride, the anhydride of a dibasic acid, in the manner formulated. As the *para* carbon atom becomes bonded to the carbonyl group, the *para* hydrogen opens the anhydride ring to produce a carbonyl group. The product has a *p*-chlorobenzoyl group, p-ClC_6H_4CO—, attached to the β-carbon atom in propionic acid. In this reaction the yield, checked in different laboratories, is only 45%, whereas under the same conditions the yield of β-benzoylpropionic acid from benzene is 90%, and the difference can be attributed to the weakly inductive effect of the chlorine substituent.

6.13

Electron-releasing groups exert an inductive effect of the opposite

nature and facilitate substitution in the benzene ring, since displacement of electrons into the ring increases electron density at the available centers and thus activates them for electrophilic attack. The methyl group, recognized as electron-releasing from the fact that it enhances the rate of bromination of ethylene (3.14), is a weakly activating group. The inductive effect of other activating groups cannot be evaluated from data for aliphatic compounds because of the



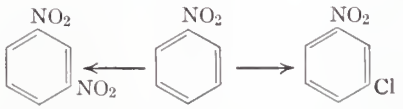
Aniline	Phenol	Phenylacetate	Toluene
1.58	1.61	1.52	0.41

Dipole moment of group

Electron-releasing, activating groups

resonance effect described below, but can be estimated from the dipole moments. Thus the amino group of aniline and the hydroxyl group of phenol are very potent activators, and, in comparison with these groups, methyl is seen to be very weak.

Directive Effect of Groups. — Groups of one type direct the entering substituent into the *meta*-position, or are *m*-directors. The nitro group is of this type and nitrobenzene on further nitration yields *m*-dinitrobenzene; on chlorination it yields the *m*-chloro derivative, 6.14



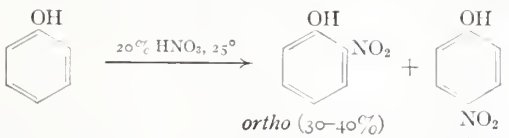
m-Dinitrobenzene *m*-Nitrochlorobenzene

and the product of sulfonation is *m*-nitrobenzenesulfonic acid. Other *meta*-directing groups are as listed:

—NO_2 —SO_3H(Na) —$COCH_3$ —$COOCH_3$ —COOH —CHO

meta-Directors

Groups of a second type cause the substituent to enter either the *ortho*- or *para*-position, or both, and these are called *op*-directors. Direction to the *para*-position is usually stronger than *ortho*-direction,



ortho (30–40%) *para* (14%)

and often only the *para*-isomer is produced. All *meta*-directing groups

—NH_2 —OH —OCH_3 —$OCOCH_3$ —CH_3 —Cl —C_6H_5

very powerful

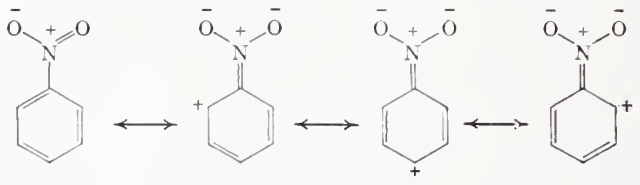
op-Directors

are also deactivators, and most *ortho-para* directing groups have an activating inductive effect; chlorine has a deactivating effect but nevertheless directs substitution to *op*-positions. Thus direction of substitution is not determined by the nature of the inductive effect.

6.15 ✳

The factor determining the direction of substitution appears in most instances to be a resonance effect. Nitrobenzene (a) is regarded as a resonance hybrid involving three other structures (b–d). An

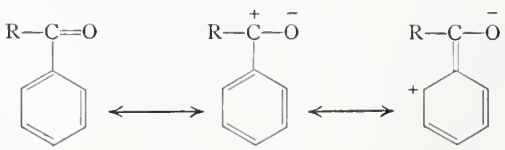
Resonance determines direction



(a) (b) (c) (d)

initial charge separation in (a) involves opening of the double bond to oxygen and one bond of the benzene ring, with appearance of a new double bond between nitrogen and the ring and of a negative charge on oxygen and a positive charge at one of the *ortho*-positions of the ring (b). This positive charge can be redistributed to the *para*-position (c) and to the second *ortho*-position (d), but a structure with the charge at the *meta*-position is not possible. The effect of resonance in nitrobenzene is to set up positive centers at the *ortho*- and *para*-positions, and hence to render these sites particularly inaccessible to electrophilic agents; the *meta* carbon atoms are deactivated by induction, along with the rest, but at least offer better points for attack than *ortho-para* positions. Thus nitrobenzene is nitrated with difficulty because of inductive repulsion of $^{+}NO_2$ and the orientation is *meta* in consequence of resonance. Benzenesulfonic acid offers the same opportunity for resonance as nitrobenzene. In the case of a carbonyl-containing group (e), initial charge separation (f) is promoted by distribution of the positive charge into the ring as in (g), which is one of three equivalent structures.

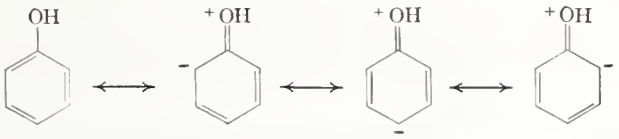
Positive charge distributed in ring



(e) (f) (g)

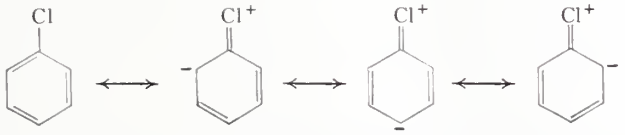
6.16

In phenol, resonance is possible, but it involves charge separation in the sense opposite to that involved with *meta*-directing groups. The oxygen atom has two pairs of unshared electrons and one pair can move in to form a double bond, leaving the oxygen positively charged. A balancing negative charge distributed among the *ortho*- and *para*-



Negative charge distributed in ring

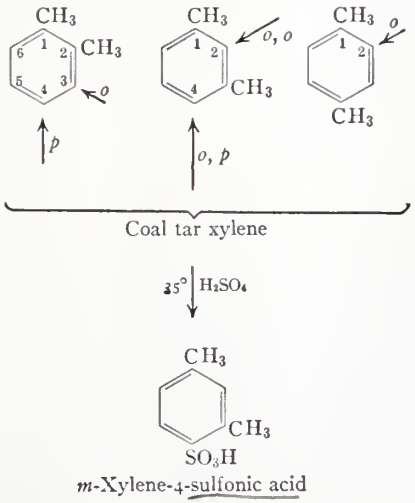
positions increases the electron density at these centers and results in *ortho-para* substitution. Replacement of the phenolic hydrogen by methyl or acetyl does not influence the direction of substitution as determined by resonance. The amino group, like hydroxyl, has a key atom with unshared electrons, and resonance structures of an analogous type determine *op*-substitution. In chlorobenzene, resonance again



Chlorine, a deactivator, but directs op

establishes electron-rich centers at *ortho-para* positions and determines the course of substitution. The Friedel-Crafts reaction of chlorobenzene with succinic anhydride cited above in illustration of the weak inductive effect of chlorine also illustrates the directive effect, since the substance formed is the *para*-isomer. The *op*-direction of the methyl group cannot be explained by resonance of the usual type and still presents a problem. However, the directive effect of this group, like its inductive effect, is weak; thus on nitration of toluene, some *m*-nitrotoluene is formed along with the *o*- and *p*-isomers.

Application of the Rules of Substitution. — The rules stated above regarding the inductive and directive effect of groups make possible in many instances prediction of the outcome of a given reaction. In *o*-xylene only two positions, C_3 and C_4, are available for substitution, 6.17



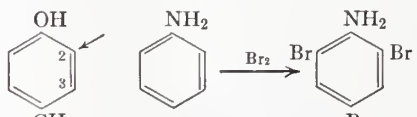
m-Xylene-4-sulfonic acid

since C_6 is the same as C_3 and C_5 is the same as C_4. Since alkyl groups facilitate substitution and are *op*-directing, one methyl group tends to promote *o*-substitution at C_3 and the other exerts a somewhat stronger *p*-direction to C_4. In *m*-xylene there are two *o*-directions to C_2 and one *o*- and one *p*-direction to C_4, and there is no direction to the only alternate position C_5. In *p*-xylene only one substitution product is possible, since all free positions are identical, and this lone site is influenced by only one *o*-direction. The lengths of the arrows represent the relative intensities of the effects, and it will be seen that the most reactive site in any of the three molecules is C_4 in *m*-xylene, which is activated by one *o*- and one *p*-effect. *p*-Xylene should be the least reactive isomer. These predictions are substantiated by various experimental observations, one of which is that when the xylene mixture from coal tar is shaken with 80% sulfuric acid at 25° the *meta* isomer slowly dissolves with formation of *m*-xylene-4-sulfonic acid. Another is that the xylene mixture can be partially sulfonated with 84% acid to leave a residue of unreacted hydrocarbon greatly enriched in *p*-xylene. *o*-Xylene, as expected, is sulfonated chiefly at the 4-position.

Reactivity: m > o > p

6.18 If two groups of the same type occupy *para*-positions, they compete with each other. An example is *p*-cresol, in which hydroxyl

Competition between groups

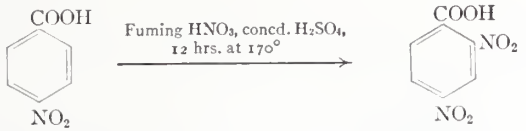


p-Cresol — 2,4,6,-Tribromo-aniline

directs to C_2 and the methyl group to C_3. Since hydroxyl is the more potent group of the two, position 2 is the point of attack in bromination, nitration, and sulfonation. Aniline, with the powerfully *op*-directing amino group, reacts so readily with bromine, even in very dilute aqueous solution, that all three *op*-positions are substituted by bromine. A competition is involved here, because once bromine has entered any of the three positions it tends to direct a subsequent bromine into a position *meta* to the amino group. The effect is so much weaker than that of the amino group that the bromines are forced to assume positions *meta* to each other.

Powerful op-direction of —NH_2

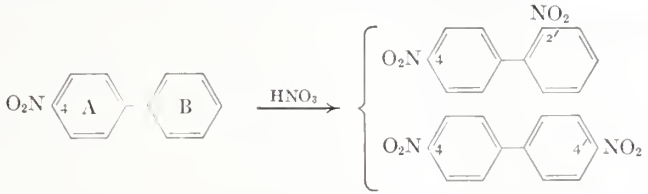
6.19 *p*-Nitrobenzoic acid presents a case of competition in a negative sense, since each group tends to give rise to resonance structures with the positive charge distributed in the positions *ortho* to the group and hence to prevent substitution in those positions. Since the nitro group is the more powerful of the two, substitution occurs *ortho* to the carboxyl group. That the reaction proceeds only with



2,4-Dinitrobenzoic acid
(m.p. 182°)

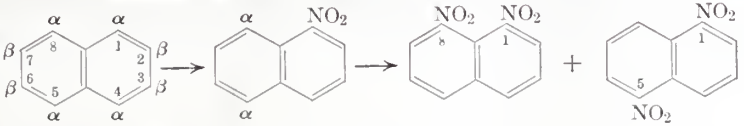
Competition between m-directors

considerable difficulty is indicated by the conditions cited in the formulation. A related case arises in compounds substituted in one



Substitution in ring that is not deactivated

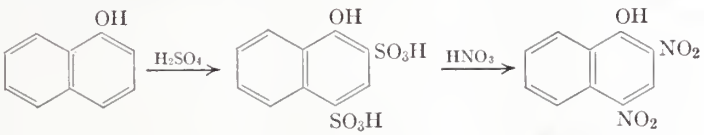
of two benzene rings, for example, 4-nitrodiphenyl. One ring (A) is deactivated by the nitro group whereas the other (B) is not, and hence the latter ring is the one attacked. Since the *p*-nitrophenyl group, like phenyl, is *op*-directing, nitration gives a mixture of the 2′- and 4′-nitro derivatives. Naphthalene on nitration is converted



α-Nitronaphthalene

Preference for α-substitution

in good yield into the α-nitro derivative. On further reaction the second nitro group enters both α-positions of the ring that is not deactivated. In α-naphthol the hydroxyl group facilitates substitution in the ring to which it is attached, and substitution occurs at the *ortho*- and *para*-positions, 2 and 4. Since phenols are sensitive to



α-Naphthol Martius Yellow

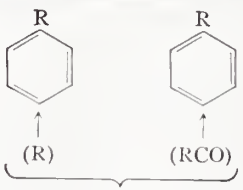
Nitration via sulfonation

oxidation and nitric acid is a strong oxidizing agent, it is best to introduce nitro groups via sulfonic acid groups. Thus 5 g. of α-naphthol is treated with 10 ml. of concentrated sulfuric acid and the mixture heated on the steam bath until the 2,4-disulfonic acid separates to form a stiff paste. This is dissolved in water and the solution is cooled and treated with nitric acid. Under the powerful activation of the hydroxyl group, displacement of sulfonic acid groups by nitro groups proceeds readily even in the dilute solution. Brief warming

on the steam bath completes the reaction, and on dilution with water the 2,4-dinitro-1-naphthol is in a form ready to be collected by suction filtration; yield 7.7 g. (88.5%).

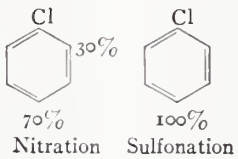
6.20 *Ortho*-Effect. — In *op*-directed sulfonations and Friedel-Crafts reactions, but not in nitrations or brominations, substituents tend to avoid the *ortho*-position, particularly if the directing group is sizable or if the reaction is done at a high temperature. Thus the chief products of the two substitutions cited are the *para*-isomers. Friedel-

Preference for p-substitution



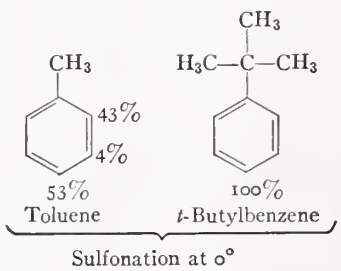
Crafts alkylation or acylation of an alkyl benzene at low temperatures affords in high yield the *p*-derivative. The Friedel-Crafts reaction of chlorobenzene with succinic anhydride cited in paragraph 6.12 is another example of *para*, rather than *ortho-para* substitution.

6.21 Comparison of the results of a quantitative study of the proportion of isomers formed on nitration and on sulfonation of chlorobenzene shows that the latter reaction is subject to a striking *ortho*-effect.



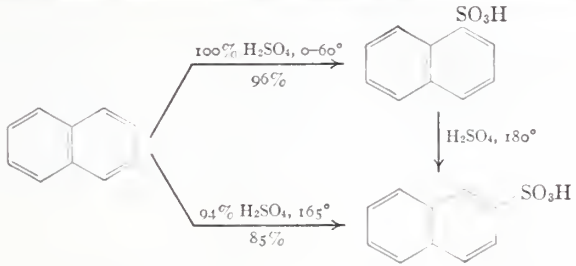
Toluene is sulfonated to about the same extent in the *o*- and *p*-positions at 0°, whereas *t*-butylbenzene yields only the *p*-isomer. The sul-

Large group shields o-position



fonic acid group avoids the position next to the bulky *t*-butyl group evidently because there is not room enough; this position is sterically hindered. Thus the extent of steric hindrance depends upon the size of the group exerting the *ortho*-effect. A rise in reaction temperature

increases collision of nearby groups and enhances the *ortho*-effect. The course of the nitration of naphthalene (6.19) shows that the α-position is more reactive than the β-position; the relationship is understandable, since the α-position is activated by the adjacent benzene ring. The α-position, however, is the more hindered position because of the proximity of this second ring. Thus at a low tempera-

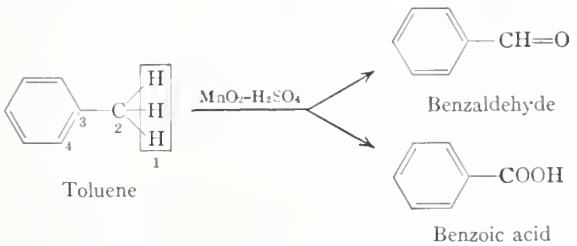


Effect of temperature

ture the hydrocarbon is sulfonated at the more reactive α-position, but at a high temperature the group is displaced to the less hindered β-position.

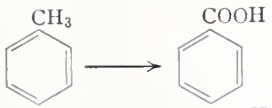
TRANSFORMATIONS OF AROMATIC COMPOUNDS

Toluene, available from coal tar, can be converted by mild oxidation into benzaldehyde, or by drastic oxidation into benzoic acid. ——— 6.22



Attack of activated hydrogens

Both reactions involve attack of hydrogen atoms in position 1, activated by the 3,4-double bond, or, more properly, by the unsaturated, resonant phenyl group. Thus benzaldehyde, the initial product, may arise by the sequence: $C_6H_5CH_3 \longrightarrow C_6H_5CH_2OH \longrightarrow C_6H_5CH(OH)_2 \longrightarrow C_6H_5CHO$. Alkylated derivatives of benzene are generally oxidizable to carboxylic acids. Thus *p*-xylene on oxida-

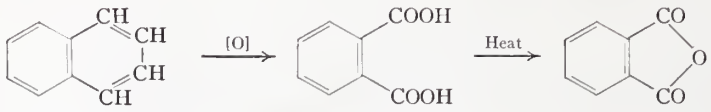


p-Xylene — Terephthalic acid

tion with permanganate or with dilute nitric acid affords terephthalic acid in high yield. Phthalic acid, the *o*-isomer, is so named because

the first practical source was oxidation of the abundant coal-tar constituent naphthalene (naphthalene + ic). In the modern vapor-

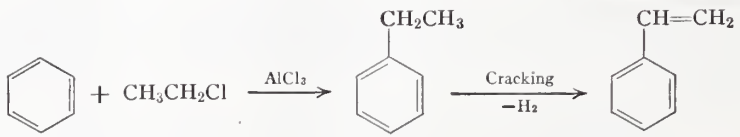
Production of phthalic anhydride



Naphthalene — Phthalic acid — Phthalic anhydride

phase method, naphthalene vapor is passed with air over vanadium pentoxide catalyst on silica gel at 470°, at which temperature the acid is cyclized to the anhydride, which sublimes into the condenser in pure form. Both terephthalic acid and phthalic acid are of value for the production of plastics and resins by methods to be described later. So is styrene, a hydrocarbon available by Friedel-Crafts ethylation of benzene and cracking, which in this case involves pyrolytic

Styrene by cracking

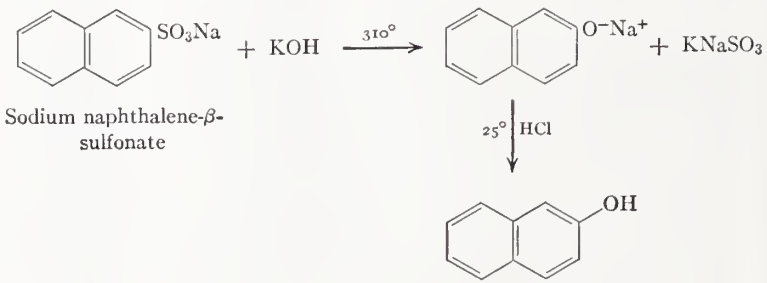


Styrene

elimination of a molecule of hydrogen and formation of a double bond.

6.23 The most widely applicable method of preparing phenols is by fusion of sulfonates with molten potassium hydroxide in the temperature range 290–320°; thus sodium naphthalene-β-sulfonate yields β-naphthol. Since glass is attacked rapidly by alkali at the tempera-

Alkali fusion of a sulfonate



Sodium naphthalene-β-sulfonate — β-Naphthol

ture required for displacement of the sulfonate group, the fusion is done in a metal container, for example, a copper beaker (a). The beaker is charged with 120 g. of potassium hydroxide pellets and 5 ml. of water (to facilitate melting) and heated over a Bunsen burner. The mixture is stirred with a mechanically driven copper stirrer, and the temperature is observed with a thermometer encased in a protective



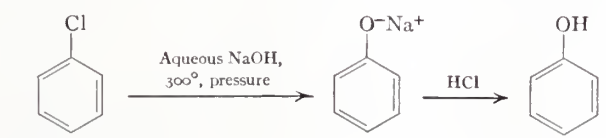
(a) (b) (c)

copper tube closed at the lower end. When the alkali melts and the temperature has risen to 250°, 50 g. of thoroughly dry sodium naphthalene-β-sulfonate is added to the stirred melt. As the temperature is gradually raised, fusion begins with some frothing. At about 300° the mass suddenly separates to a clear, mobile yellow oil of the potassium salt of β-naphthol floating on a clear melt of alkali. The temperature is raised to 310° for a few minutes, and the melt is then poured out in portions onto a slanting copper plate (b) and let solidify in scales that are let cool and then scraped off and dissolved in water, with addition of ice as required. The solution is filtered, if not clear, and acidified, when β-naphthol separates as a white precipitate; yield 24.2 g.

6.24

Phenol, required on a huge scale for conversion into dyes, explosives, and plastics, was formerly manufactured by the alkali fusion process. However, chlorobenzene can be made by catalyzed chlorination of benzene at a cost well below the cost of preparation of sodium benzenesulfonate, and the Dow Chemical Company developed a practical method for conversion of chlorobenzene into phenol. Although the chlorine atom is very unreactive, hydrolysis to phenol is realized by treating chlorobenzene with 7% aqueous sodium hydroxide

Dow process



Chlorobenzene Phenol

at a temperature of 300° and a pressure of 2500 lbs./sq. in. The hydrolysis is carried out in a continuous process by flowing the reactants through a pipe line capable of maintaining the high temperature and pressure required and of suitable length (about one mile)

to provide the period required for reaction (about twenty minutes). As initially developed, the process was efficient except for the formation of an undesired by-product, diphenyl ether, $C_6H_5OC_6H_5$. Dow salesmen distributed samples in the hope that some use for the by-product would be forthcoming, but none materialized. Even disposal of the by-product as waste presented a problem. Then Dow research chemists established that diphenyl ether is formed in a reversible equilibrium reaction:

Problem of a by-product

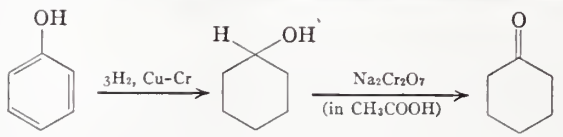


Diphenyl ether

They then found, as expected, that the unwanted by-product can be kept from accumulating by simply recycling the amount necessary to meet the equilibrium requirement.

6.25 One important use for phenol is for preparation of cyclohexanol. The benzene ring is not very reactive to additions, but under forcing

Cyclohexane derivatives

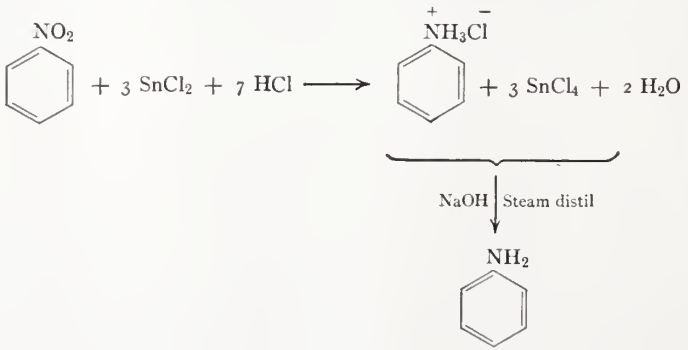


Phenol Cyclohexanol Cyclohexanone

conditions hydrogenation can be effected satisfactorily and in high yield. Cyclohexanol made by hydrogenation of phenol is the starting material for the production of nylon fiber. It yields cyclohexanone on oxidation.

6.26 Nitration provides an efficient route to aromatic amines, or aryl amines, since nitro compounds are readily reduced in high yield. Nitrobenzene can be reduced, for example, with stannous chloride and hydrochloric acid to give a solution of aniline hydrochloride and

Preparation of aniline



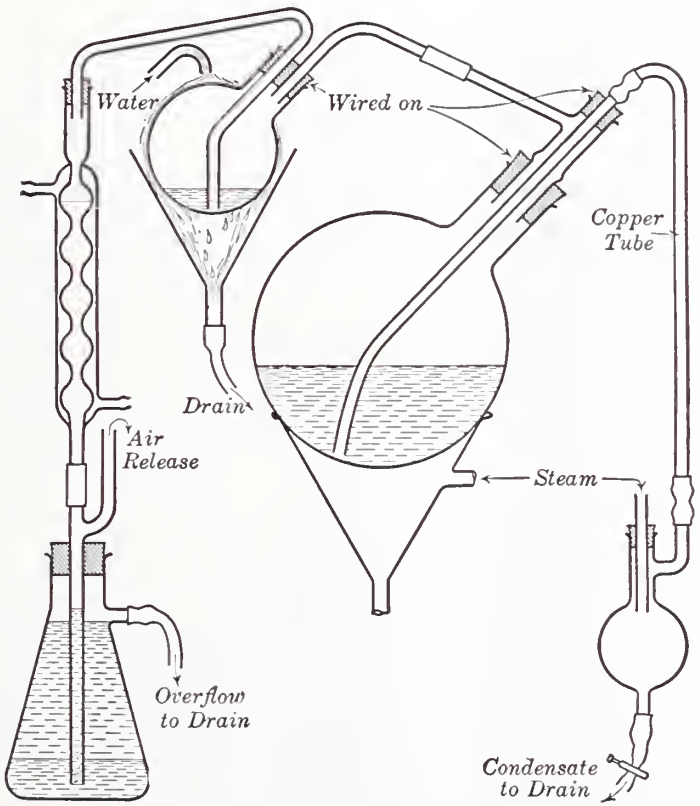
Aniline, b. p. 184°

stannic chloride. Alkali is added to liberate aniline and dissolve the tin derivative as sodium stannate (Na_2SnO_3), and the aniline is removed from the mixture by steam distillation.

6.27

Theory of steam distillation

The principle of steam distillation of a substance insoluble in water, or, like aniline, only partially soluble, is as follows. As the temperature is raised, each substance, water and aniline, exerts a progressively increasing vapor pressure in opposition to the pressure of the atmosphere. Since the two substances do not dissolve, and hence do not dilute each other, each exerts its normal vapor pressure independently. The total vapor pressure in the flask is the sum of the partial vapor pressures of the components. The vapor pressure of water at 100° equals that of the atmosphere, which under normal conditions is 760 mm. of mercury; the vapor pressure of aniline reaches 760 mm. only at a temperature of 184°. It is evident, however, that in the temperature range of 90–100°, water has a vapor pressure not far short of 760 mm. and aniline has a small but appreciable vapor pressure. Since the two partial pressures are additive, a mixture of aniline and water must reach the total vapor pressure



Efficient apparatus for steam distillation

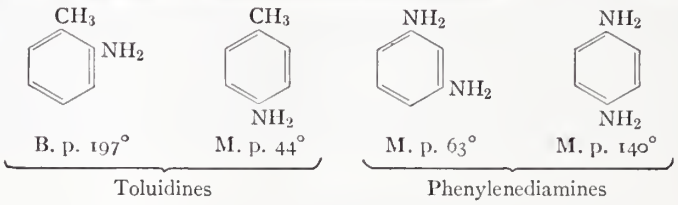
Steam distillation of aniline (the heavy liquid collecting in the filter flask)

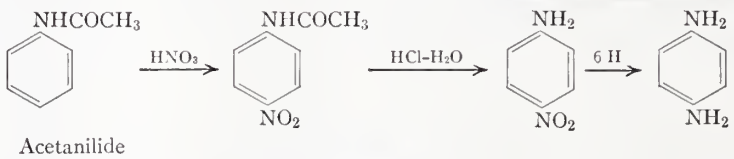
of 760 mm. necessary for boiling at a temperature somewhat lower than 100°. Hence steam, freed of excess water by a condensation trap such as that shown in the drawing and passed into a flask containing the alkalinized reduction mixture, entrains aniline and carries it over into the receiving flask at a temperature below 100° (98.5°). Steam distillation can be conducted very rapidly in the apparatus shown because the small flask, cooled with a stream of water, provides a liquid seal, or vapor trap, insuring efficient condensation; vapor from the distillation flask has to bubble through condensate in the small flask and so is induced to condense.

6.28

Other aryl amines

The *o*- and *p*-derivatives of aniline, *o*- and *p*-toluidine, are made by similar reduction of *o*- and *p*-nitrotoluene, available by nitration of toluene and separation by fractional distillation. The diaminobenzenes are known as phenylenediamines. The *m*-isomer results from dinitration of benzene and reduction, and the *p*-isomer is obtainable in high yield by nitration of acetanilide, the N-acetyl derivative of aniline, hydrolysis of the product, and reduction of the resulting *p*-nitroaniline; advantage is thus taken of the almost exclusive *p*-direction of the acetylamino group. From the physical properties cited above under the formulas, it will be seen that *p*-toluidine is a solid and *o*-toluidine a liquid, and that *p*-phenylenediamine has a higher melting point than the *m*-isomer; the isomers of greater symmetry have the higher melting points.





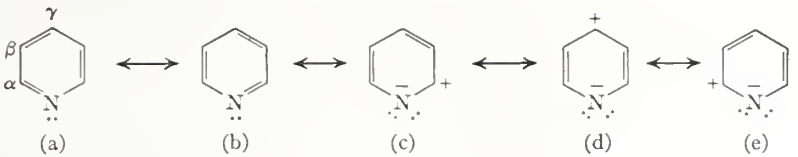
Symmetry and m.p.

HETEROCYCLIC AROMATICS

6.29

The resonance energy of pyridine is 43 kg.-cal./mole, significantly higher than that of benzene (36 kg.-cal.). In this heterocycle the possibility for resonance extends beyond the two identical Kekulé structures (a) and (b) to three additional structures (c–e), in which the relatively electron-attracting nitrogen atom acquires an additional pair of electrons from a carbon atom in the α- or γ-position,

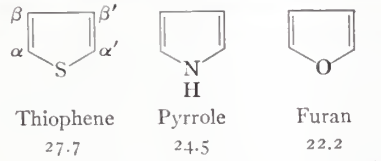
Pyridine superaromatic



which thereby becomes positively charged. Thus electrophilic substitution occurs only at the β-position. Actually, such substitution is realizable only under forcing conditions. Bromination can be accomplished only in the vapor phase at a temperature of about 300°, and sulfonation and nitration can be effected only under forcing conditions. Attempted Friedel-Crafts reactions are invariably negative. Thus pyridine corresponds in aromaticity to nitrobenzene rather than to benzene.

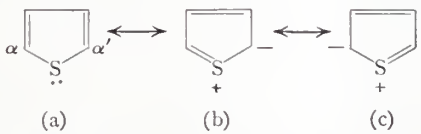
The five-membered heterocycles thiophene, pyrrole, and furan can be seen from their resonance energies to be less aromatic than benzene but nevertheless resonance-stabilized. Stabilization cannot

6.30



be achieved as in benzene and pyridine by resonance involving two equivalent Kekulé structures, but the hetero atom is responsible for an evidently weaker resonance effect. In thiophene (a) displacement of a pair of unshared electrons of the sulfur atom to one adjacent carbon atom, with separation of charge, gives structure (b), and displacement to the other α-carbon gives (c). Structures (b) and (c),

Resonance stabilization



with centers of high electron density at α-positions, account for the fact that thiophene is substituted in electrophilic reactions in the α-position. That such substitutions occur more easily than in the case of benzene is shown by the fact that Friedel-Crafts reaction of acetyl chloride with thiophene can be effected with the mild catalyst zinc chloride; aluminum chloride is liable to cause resinification. Coal-tar benzene can be freed of thiophene by shaking it in the cold with concentrated sulfuric acid; thiophene is sulfonated preferentially and is removed with the acid. Since the hetero atoms of pyrrole and

of furan carry unshared electrons, resonance stabilization is achieved in the same way as with thiophene.

SUMMARY

Structure and Source

Faraday (1825): isolation of benzene from coal gas. Mitscherlich (1834): benzene by decarboxylation of benzoic acid (from gum benzoin, origin of name). Hofmann (1845): coal tar a practical source. Perkin (1856): first synthetic dye from a coal-tar hydrocarbon. Kekulé (1865): cyclic structure deduced from the number of substitution products; one mono, three di, three tri.

Kekulé cyclohexatriene formula later confirmed and interpreted: a resonance-stabilized hybrid. X-ray analysis shows all six bonds to be of identical length, 1.40 Å. Resonance energy of benzene 36 kg.-cal./mole (cf. butadiene, 3.5 kg.-cal.). Six ring carbons and six peripheral hydrogens all coplanar.

Hydrocarbons from coal tar: benzene, toluene, xylenes, diphenyl, naphthalene (2 fused rings), anthracene (three rings fused in a line). Heterocyclic components: pyridine (six-ring containing nitrogen), quinoline (pyridine ring fused to a benzene ring), thiophene (five-ring containing sulfur).

Aromatic Substitutions

Substitution is the rule, rather than addition. Ferric bromide-catalyzed bromination interpreted as an attack by the electrophile Br^+ of $Br^+FeBr_4^-$ to give a carbonium ion from which $FeBr_4^-$ removes H^+ to form bromobenzene. Nitration involves attack by NO_2^+, produced in a mixture of HNO_3 and H_2SO_4. Sulfonation: attack by SO_3, which contains two semipolar bonds. Friedel-Crafts alkylation and acylation involve similar attack by cations: CH_3^+ and $CH_3C^+{=}O$, from $CH_3^+AlCl_4^-$ and $CH_3C^+{=}O[AlCl_4]^-$.

Deactivating inductive effect: a positively charged or other electron-attracting group decreases electron density in ring and hence decreases susceptibility to electrophilic attack. $C_6H_5NO_2$, $C_6H_5COCH_3$, $C_6H_5CO_2R$ are nitrated less easily than C_6H_6 and do not undergo Friedel-Crafts reaction. Chlorine a less potent deactivator; C_6H_5Cl can be succinoylated, but in poor yield. Activating inductive effect: electron-releasing groups ($-NH_2$, $-OH$, $-OCOCH_3$, $-CH_3$) facilitate substitution.

Resonance effect. *m*-Directors: $-NO_2$, $-SO_3H$, $-COCH_3$, $-COOCH_3$, $-CHO$. *op*-Directors: $-NH_2$ and $-OH$ very powerful; $-OCH_3$, $-OCOCH_3$, $-CH_3$, $-Cl$, $-C_6H_5$. Resonance structures of nitrobenzene with *op*-positions carrying positive charge and hence inaccessible to electrophilic attack. Resonance in carbonyl compounds similarly determines *m*-attack. In resonance structures of phenol and aniline, *op*-positions are negatively charged and hence vulnerable to attack. Halogen atoms *op*-directing (resonance), but deactivating (induction).

Predicted order of reactivity of the xylenes: $m > o > p$. Demonstrated in sulfonations. Competition between two *p*-groups: $OH > CH_3$, $NH_2 > Br$, $NO_2 > CO_2H$. *p*-Nitrodiphenyl is substituted in ring not deactivated by $-NO_2$. Naphthalene mononitrated in more reactive α-position; second nitro group enters both α-positions of ring not deactivated. α-Naphthol forms the 2,4-disulfonate; on subsequent nitration, the sulfonic acid groups are displaced by $-NO_2$ groups to give a dye, Martius Yellow.

ortho-Effect. In sulfonations and Friedel-Crafts reactions entering group avoids hindered *o*-positions. *p*-Product thus predominates in F.-C. alkylations and acylations; in sulfonation of C_6H_5Cl, as compared to nitration; in sulfonation of *t*-butyl benzene (bulky group). Naphthalene sulfonated at 0–60° in reactive but hindered α-position; at 165° the β-sulfonic acid is formed.

Transformations

$C_6H_5CH_3 \longrightarrow C_6H_5CHO \longrightarrow C_6H_5CO_2H$. *p*-Xylene $\longrightarrow$ terephthalic acid. Naphthalene $\longrightarrow$ phthalic anhydride. $C_6H_6 + CH_3CH_2Cl$ $(AlCl_3) \longrightarrow C_6H_5CH_2CH_3 \longrightarrow$ (by cracking) $C_6H_5CH{=}CH_2$ (styrene). Alkali fusion of a sulfonate gives a phenol (e.g. β-naphthol). Dow continuous process for making phenol. Problem of the by-product, $C_6H_5OC_6H_5$, and its solution. Phenol a source of cyclohexanol and cyclohexanone. Aniline by reduction of nitrobenzene and steam distillation. Toluidines (*o* and *p*) from nitrotoluenes. Benzene $\longrightarrow$ m-$C_6H_4(NO_2)_2 \longrightarrow$ m-$C_6H_4(NH_2)_2$ (*m*-phenylenediamine). $C_6H_5NHCOCH_3 \longrightarrow$ p-$NO_2C_6H_4NHCOCH_3 \longrightarrow$ p-$NO_2C_6H_4NH_2 \longrightarrow$ *p*-phenylenediamine.

Pyridine superaromatic; resonance energy 43 kg.-cal./mole (benzene 36). Resonance between identical Kekulé structures reinforced by charge separation, with N negative and α- and γ-positions positive. Explains β-substitution under forcing conditions. Five-membered heterocycles: thiophene (S), pyrrole (NH), furan (O). Less aromatic than benzene because stabilized only by resonance involving charge separation. Negative α-position the point of attack by an electrophile.

PROBLEMS

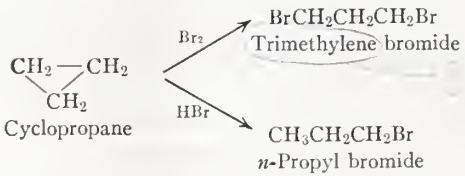
1. Predict the chief products of the following reactions:
   (*a*) Nitration of resorcinol dimethyl ether (1,3-dimethoxybenzene)
   (*b*) Monobromination of
   p-$CH_3CONHC_6H_4OCOCH_3$
   (*c*) Sulfonation of p-cymene,
   p-$CH_3C_6H_4CH(CH_3)_2$
   (*d*) Sulfonation of p-methylacetophenone,
   p-$CH_3C_6H_4COCH_3$
   (*e*) Nitration of phenol-p-sulfonic acid
   (*f*) Condensation of 1,2,4-trimethylbenzene with acetyl chloride in the presence of aluminum chloride
   (*g*) Nitration of m-dichlorobenzene
   (*h*) Friedel-Crafts condensation of succinic anhydride with desoxybenzoin,
   $C_6H_5COCH_2C_6H_5$
   (*i*) Nitration of diphenylmethane-p-carboxylic acid
   (*j*) Friedel-Crafts methylation of p-chlorodiphenylmethane
   (*k*) Mononitration of 4-methyl-4′-hydroxydiphenyl
2. Suggest methods for the Friedel-Crafts synthesis of (*a*) t-butylbenzene, (*b*) p-di-t-butylbenzene.
3. How could p-$(CH_3)_3CC_6H_4CO_2H$ be synthesized starting with toluene?
4. Naphthalene on oxidation gives phthalic acid (or anhydride). Would you expect α-nitronaphthalene to be oxidized to phthalic acid or to 3-nitrophthalic acid?
5. What product would you expect to result from the oxidation of isopropylbenzene?

CHAPTER 7

CYCLOALKANES

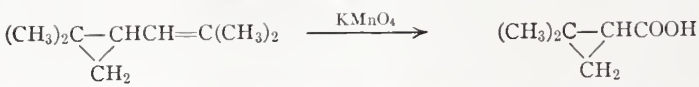
7.1 **Reactivity.** — Cyclopropane is a saturated hydrocarbon, but it nevertheless exhibits considerable reactivity. Indeed the three-membered ring tends to open the way the double bond of ethylene opens. Thus cyclopropane reacts with bromine to form trimethylene

Cyclopropane reacts like ethylene

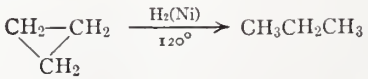


bromide and it reacts with hydrogen bromide to give *n*-propyl bromide, and in these respects it resembles ethylene. However, unlike ethylene, cyclopropane is not attacked by potassium permanganate. An interesting demonstration that a double bond is indeed more reactive than a three-carbon ring is that a hydrocarbon having both functions is oxidized only at the double bond. Further evidence is that in the

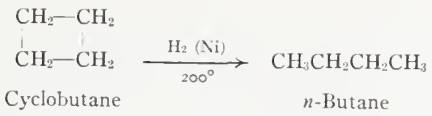
But is somewhat less reactive



presence of Raney nickel catalyst ethylene can be hydrogenated to ethane at 25°, whereas cyclopropane is hydrogenated satisfactorily only at 120°.



7.2 That cyclobutane is less reactive than cyclopropane is shown by its failure to react with either bromine or hydrogen bromide. The only way the cyclobutane ring has been opened is by catalytic hydro-



Cyclobutane — *n*-Butane

genation. Even so the Raney nickel-catalyzed reaction proceeds only at a high temperature, 200°. Cyclopentane exhibits no reactivity whatsoever and cannot be hydrogenated under any known conditions. Indeed cyclopentane is just as inert chemically as *n*-pentane, and the same is true of cyclopentane derivatives in general.

Cyclopentane inert

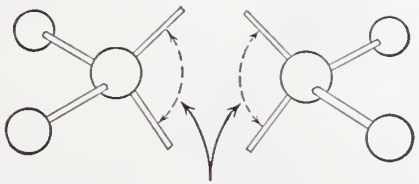
Baeyer Strain Theory. — A theoretical interpretation of the difference in reactivity of hydrocarbons of various ring size was advanced in 1885 by Baeyer. Baeyer noted that if the four valences of the carbon atom are directed toward the corners of a regular tetrahedron the normal angles between any two linkages is 109° 28′, and he postulated that any deviation from this angle would result in internal strain in

7.3

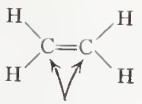


Adolf von Baeyer, 1835–1917
Born Berlin; Ph.D. Berlin; Universities of Strasbourg and Munich; Nobel Prize 1905 (Ph.D. theses of Baeyer's students at Munich carried the standard acknowledgment to "Seiner Exzellenz Herr Geheimrat Professor Dr. Adolf Ritter von Baeyer," or "His Excellency Mr. Privy Councillor Professor Doctor Adolf, Knight of the family Baeyer.")

the molecule. The linking of two carbon atoms by a double bond is attended with considerable angle distortion, with consequent strain



Normal angle = 109°28′



Angle = 0°

and high energy content, and this explains the reactivity of ethylene and the tendency of the double bond (two-membered ring) to open by

addition of various reagents. An addition relieves the strain because the product formed, an ethane derivative, has no distorted bonds. For comparison with the cycloalkanes, Baeyer calculated the bond distortion of ethylene as follows. Since the normal angle for each carbon is 109° 28′, the total distortion in a double bond, in which the angle is zero, is 109° 28′ and the distortion per carbon atom is half that, or 54° 44′. For three carbon atoms to bond together to form the cyclopropane ring, calculation shows that the bond distortion for each atom is 24° 44′. The strain theory thus accounts for the fact that cyclopropane is evidently under strain and reactive, though less reactive than ethylene. For cyclobutane the calculated distortion per carbon atom is 9° 44′, and for cyclopentane the value is 0° 44′, corresponding to a negligible strain. The Baeyer strain theory thus accounts well for the known facts.

Bond angle distortion decreases with increasing ring size

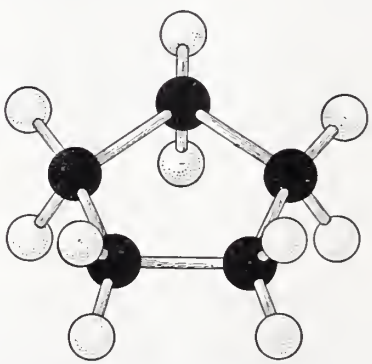
7.4 Molecular models in which steel springs are used for bonding the carbon atoms provide a crude but effective expression of relative strain. Closure of the elements of a double bond (a) requires considerable



(a) (a′) (b) (c)

compression of the springs (a′) and forms a strained molecule prone to fly open. The gap between the parts to be joined is progressively less for formation of a three-membered ring (b) and a four-membered ring (c). A model of practically strain-free cyclopentane can be constructed with wooden bonds.

Compression of spring bonds



Cyclopentane

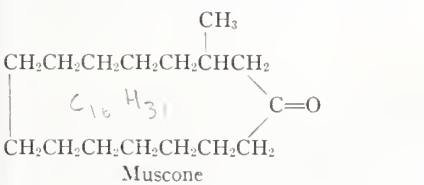
Large Rings. — When Baeyer presented his strain theory in 1885 very little was known about cyclohexane and no higher cycloalkanes were available for study. On the assumption that the six carbon atoms of cyclohexane lie in a plane, as the five carbon atoms of cyclopentane of necessity do, Baeyer considered that the bonds would have to be distended, rather than compressed, and calculated the distortion per carbon atom to be $-5° 16'$. Bond strain should then increase progressively with increasing ring size, and a very large ring should be too strained to exist. In purely theoretical papers, H. Sachse in 1890 and E. Mohr in 1918 questioned Baeyer's assumption that the carbon atoms of cyclohexane lie in a plane and pointed out that nonplanar puckered conformations are possible in which all valences have the normal tetrahedral angle. It was not until 1926, however, that experimental evidence became available regarding the actual properties of large-ring compounds. 7.5

Prediction of strain from bond distention

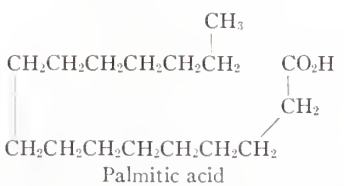
Planarity of cyclohexane questioned

This evidence stemmed from work by Leopold Ruzicka in Zurich on the active principles of the rare perfume bases musk and civet. Dried musk is a dark-colored powdery substance of powerful odor obtained from an egg-sized gland situated near the abdomen of the male musk deer, a small wild animal found in mountainous regions of central Asia, particularly the Himalayas; the apparent function of musk is to attract the female animal. From about 60,000 deer killed per year for the perfume industry, there results an average of about 2000 kg. of the valuable musk, the active principle of which, muscone, is present to the extent of about 1%. Civet, valued at about one third the price of musk, occurs similarly in the African civet cat (male and female), and the active principle is civetone. The names muscone and civetone were assigned after the substances had been isolated in pure form and characterized as ketones. By degradation to known compounds or to compounds that could be identified by synthesis, Ruzicka established that muscone has a ring of fifteen carbon atoms 7.6

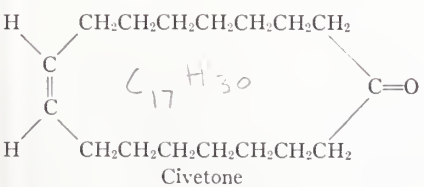
Perfume principles muscone and civetone



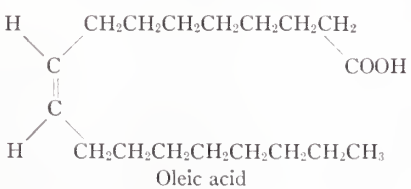
Muscone



Palmitic acid



Civetone



Oleic acid

Large-ring ketones

with a branching methyl group, and that civetone has a ring of no less than seventeen carbon atoms and a symmetrically placed double bond (*cis*-configuration). Civetone is related to oleic acid, a component of fats, both in structure and in *cis*-configuration, and muscone bears some relationship to the fat component palmitic acid. The point of importance to the present discussion is that muscone and civetone have normal properties, no special reactivity, and show no evidence of any strain. Therefore, the carbon atoms making up these large rings must be nonplanar and puckered, in accordance with the suggestion of Sachse and of Mohr.

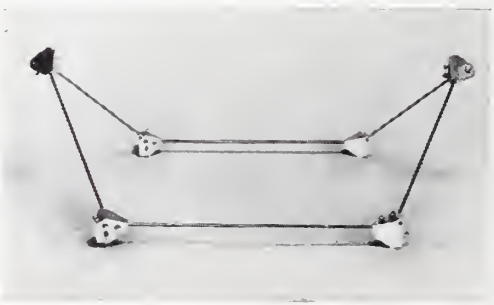
Large rings are strain-free

CONFORMATION

7.7 **Cyclohexane.** — The mechanical models available to Baeyer must have been crude. The Barton models shown in the photographs below are made of accurately machined tetrahedra of aluminum joined by steel rods held in the tetrahedra by screws which maintain the tetrahedral angles but permit free rotation about the single bonds (Derek H. R. Barton, Imperial College of Technology, London). When one investigates the joining together of six carbon models to form a ring it is found next to impossible to keep the atoms in a plane because they tend naturally to rotate about single bonds and form a puckered ring. The ring can assume either of the two conformations, or shapes, shown in the photographs. One is like a chair, with a back and a leg



Chair form

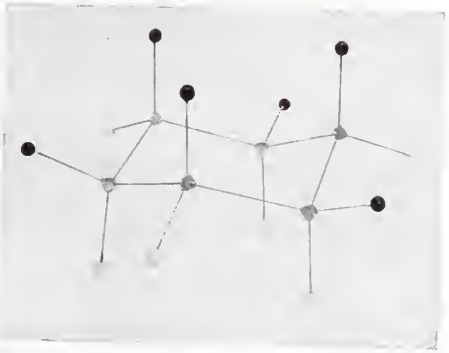


Boot form

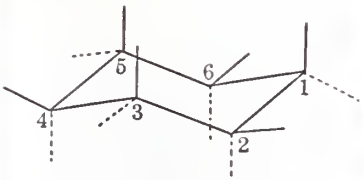
rest, and the other is like a boat, with a bow and a stern. The bond angles are all the normal 109° 28′, and both forms are free from strain resulting from bond distortion. The chair and boat forms are easily interconvertible by a slight twist to produce rotations about single bonds.

7.8 Attention should be directed particularly to the chair conformation because, as will be shown, this is more stable than the boat conformation, and is the shape preferentially assumed by all cyclohexane derivatives where a choice between chair and boat forms is open.

Attachment of twelve hydrogens to the above skeletal structure gives the complete conformational formula of chair-cyclohexane shown in the model (a). The conventional perspective representation of the model is that shown in (b); after some study of the model and the perspective representation, the latter can be used with understanding of its meaning. The actual shape of the molecule is indicated most accurately by the Stuart model (c). In both models (a) and (c)



(a)



(b)

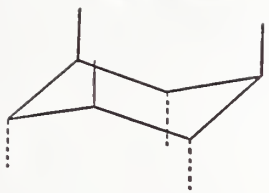


(c)

black balls represent β-hydrogen atoms, which either project straight up (C_1, C_3, C_5) or are inclined upwards with respect to the second hydrogen on the same carbon (C_2, C_4, C_6); white balls represent downward extending or inclined α-hydrogens. In (b) β-hydrogens are attached by full-line bonds and α-hydrogens by dotted-line bonds.

The β-hydrogens at C_1, C_3, and C_5 and the α-hydrogens at C_2, C_4, C_6 are all parallel to the axis of symmetry of the ring, and these six hydrogens are described as axial. The remaining hydrogens radiate equatorially and are called equatorial. The Stuart model (c) shows

7.9



Axial bonds (a)



Equatorial bonds (e)

Cyclohexane bonds (chair)

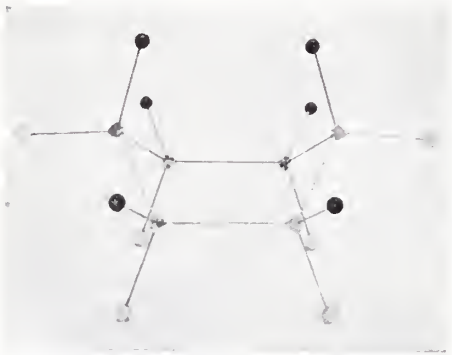
clearly the contrast of the three upper axial β-hydrogens and the nearly coplanar α- and β-equatorial hydrogens. The bunched axial hydrogens repel one another and are less accessible than equatorial hydrogens to external reagents.

The boat conformation of cyclohexane is shown in the Barton

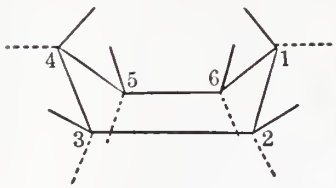
7.10

Boat conformation

model (d), the perspective formula (e), and the Stuart model (f). Four of the carbon atoms lie in a plane (2, 3, 5, 6), above which C_1



(d)



(e)

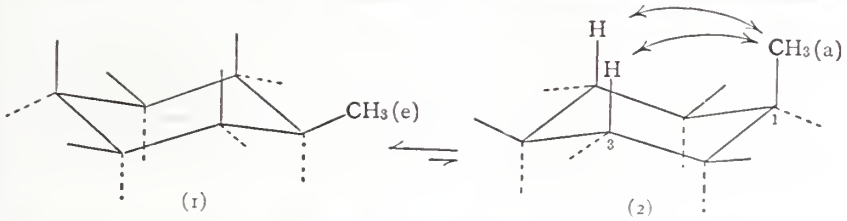


(f)

and C_4 rise to form bow and stern. The stability of the chair and boat forms is determined by the extent of the repulsive forces exerted by adjacent atoms, just as the stability of different conformations of 1,2-dichloroethane is determined by atom-repulsions. Furthermore, atom-repulsion increases exponentially as the distance separating the atoms decreases, and hence stability can be estimated from the distances separating atoms. Barton models are made to the scale that 10 cm. in the model represents 1 Å in the molecule. The chair form of cyclohexane is made up of six identical ethane units. One of these contains carbons C_1 and C_2, and it can be seen from the model (a) that the 1β-hydrogen is far away from the 2α-hydrogen but fairly close to the 2β-hydrogen. Measurement with a ruler shows the 1β–2β distance to be 25.0 cm., representing 2.50 Å in the molecule. This distance, 2.50 Å, is a measure of the severest repulsive force involved. Since there are six identical ethane units, no further measurements need be made. In the boat form (d) four ethane units are exactly like those of the chair form, namely, the 1,2-, 3,4-, 4,5-, and 6,1-units, and the hydrogen–hydrogen repulsions are expressed by the same separation distance of 2.50 Å. However, the 2,3- and 5,6-units, which form the sides of the boat, are such that the maximal separation of hydrogens is only 2.33 Å. The resultant repulsive force must be greater than any repulsive effect in the chair form. Furthermore, in the boat form the $2\beta,3\beta$-repulsion is reinforced by an identical $2\alpha,3\alpha$-repulsion. Hence the chair form is the more stable conformation of the two, and the boat form has no reality, except as part of a cage structure, for example, one formed by a methylene group bridging C_1 and C_4.

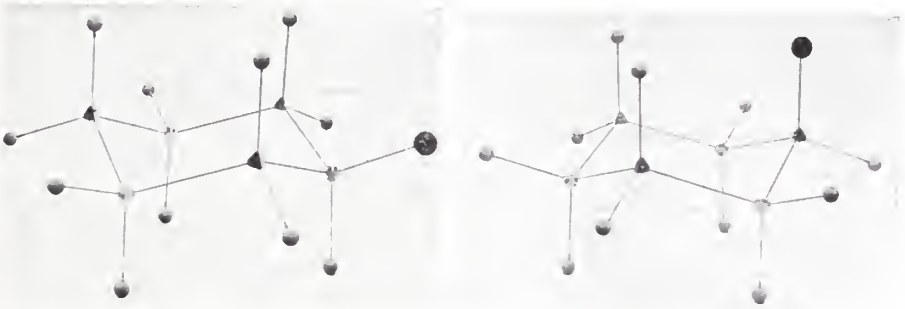
7.11 In a substituted derivative such as methylcyclohexane, two conformations are possible, one in which the methyl group is equatorial (1)

and the other in which it is axial (2). The latter is the less stable form because of repulsions between the axial β-methyl group and the axial β-hydrogens in the 1,3- and 1,3′-positions (curved arrows). These repulsions are not operative when the methyl group is equatorial,

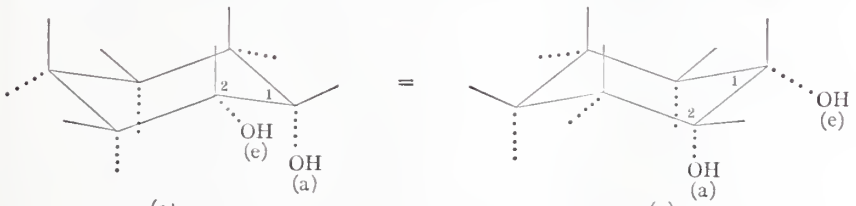


(1) (2)

Methylcyclohexane

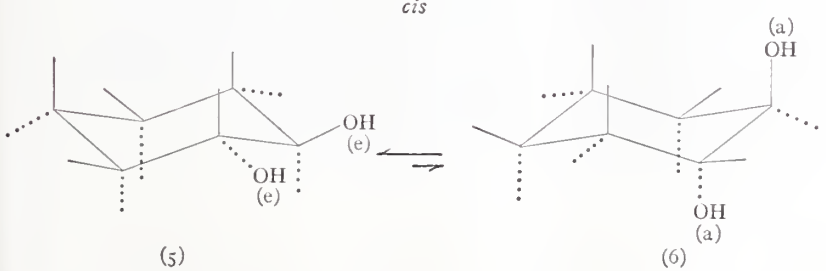


and hence (1) is the more stable form. Actually the conversion of (2) into (1) requires a mere flip of the ring, to which there is little energy barrier; axial methyl at an uptilted bow (2) becomes equatorial at a down-tilted bow (1) without losing its identity as β-oriented. In *cis*-cyclohexane-1,2-diol, formulated as the 1α,2α-diol, a ring flip



(3) (4)

cis



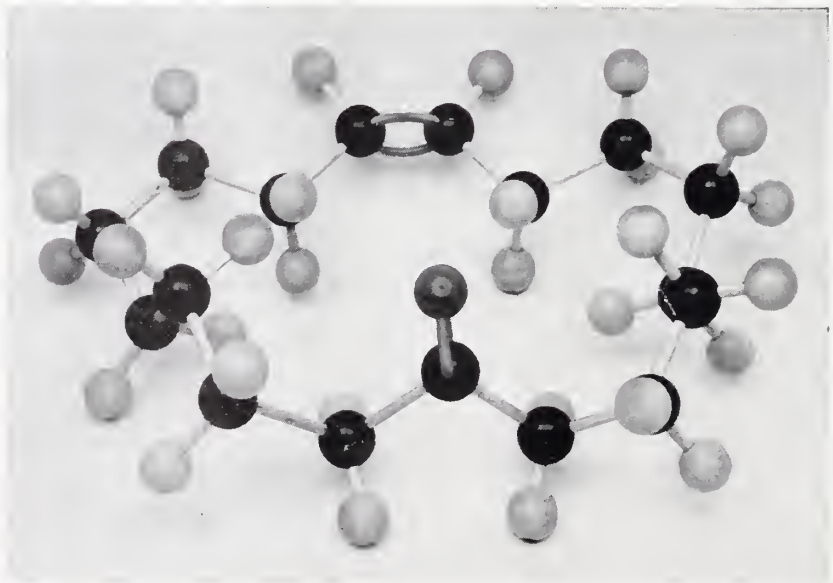
(5) (6)

trans

Cyclohexane-1,2-diols

produces no new situation, since both (3) and (4) have one axial and one equatorial hydroxyl group. In the *trans*- or 1β,2α-diol, however, one form (5) has two equatorial hydroxyl groups and the other (6) has two axial hydroxyls. The diequatorial *trans*-diol (5) is significantly more stable than the diaxial *trans*-diol (6), and also more stable than *cis*-cyclohexanediol. Since an axial hydroxyl is always close to two other axial substituents or hydrogen atoms and hence sterically hindered, axial hydroxyl groups are acetylated with greater difficulty than equatorial ones. The diequatorial diol (5), with radially located hydroxyls available for ready attack by acetic anhydride, should be acetylated more readily than the other diols formulated, and diol (6) should be the one least amenable to acetylation.

7.12 **Large Rings.** — In compounds containing very large rings, as exemplified by muscone (C_{15}-ring) and civetone (C_{17}-ring), the molecule can assume a number of conformations which are strain-free and in which the hydrogen atoms are all sufficiently far apart to eliminate any repulsive effects. Hence large-ring compounds are comparable to analogous open-chain compounds in energy content and in chemical properties. The C_{17}-ring of civetone accommodates the *cis* double bond without complications; one of the strain-free, puckered conformations is shown in the model.



SUMMARY

Reactivity. Cyclopropane adds Br_2, HBr like ethylene but is not attacked by $KMnO_4$. Ethylene hydrogenated (Raney Ni) at 25°, cyclopropane at 120°. Cyclobutane does not add Br_2 or HBr; hydrogenated to *n*-butane at 200°. Cyclopentane as inert as *n*-pentane.

Baeyer strain theory: strain due to distortion of normal carbon valence angles. Strain decreases from ethylene to cyclopropane to cyclobutane and vanishes in cyclopentane.

Large rings. Baeyer misled in assuming large rings to be strained. Prediction of puckered, strain-free rings. Muscone and civetone, fragrant principles of valued natural perfumes. Shown to have rings of fifteen and seventeen carbon atoms. Properties normal, no evidence of strain, hence prediction confirmed.

Conformation

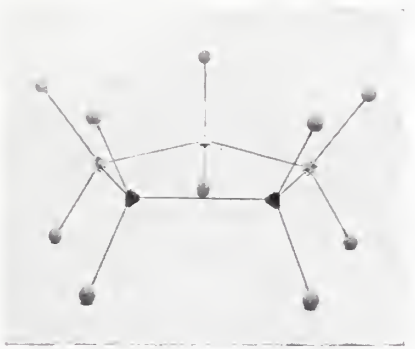
Two puckered, strain-free forms possible for six-carbon ring: chair and boat. Models and perspective formula of chair conformation. β-Hydrogens up, α-hydrogens down. Concept of axial and equatorial hydrogens.

Boat form of cyclohexane less stable because hydrogen atoms are closer together and exert repulsive force.

Methylcyclohexane more stable when methyl group is equatorial than when it is axial. Labile form ⟶ stable form by a ring flip. Stability of *cis*- and *trans*-cyclohexane-1,2-diols greatest with both hydroxyls equatorial, least when they are both axial. Equatorial hydroxyl acetylated more readily than axial hydroxyl. Large-ring compounds free from strain and from repulsive effects.

PROBLEMS

1. Cite experimental tests that would distinguish between the following isomers of the formula C_5H_{10}: pentene-2; 1,2-dimethylcyclopropane; and cyclopentane.
2. Formulate the product of osmium tetroxide hydroxylation of civetone.
3. Cyclopentane and chair-cyclohexane are both free from strain due to bond-angle distortion. However, the heats of combustion, in kg.-cal. per methylene group, are as follows: cyclopentane, 158.7; cyclohexane, 157.4. Thus cyclopentane has a slightly higher energy content than cyclohexane and is a little less stable. Compare the models and see if you can suggest any source of instability in the one which is not present in the other. (Suggestion: inspect the model of boat-cyclohexane.)



4. Which isomeric form of 1,3-dimethylcyclohexane would you expect to be the more stable, *cis* or *trans* (inspect the perspective formula 7.8b and consider all possibilities for each isomer)?

CHAPTER 8

PETROLEUM

8.1 Natural gas and petroleum, probably formed by decomposition of organic material of marine origin, occur in the interstices of granular rocks (limestones, sandstones) of the upper strata of the earth, entrapped by overlying nonporous rock (L. *petra*, rock + *oleum*, oil). When a well is drilled through the cap, oil for a time is forced to the surface until the pressure subsides and then is removed by pump. Natural gas flowing from a well consists largely of methane and gaseous homologs but contains dissolved C_5–C_7 hydrocarbons which are normally liquid and valuable as gasoline components. Consequently the raw gas is passed through an oil scrubber or a compressor for recovery of material known as natural gasoline, which was formerly blended with refinery gasoline to increase volatility. The residual gas is carried by pipeline for use as domestic or industrial fuel. Refining of petroleum, usually a dark, viscous oil, involves distillation into fractions of different boiling ranges and reprocessing of fractions, for example, by extraction of acidic and basic components. Gasoline fractions boil in the range 40–205° (kerosene, b.p. 175–325°).

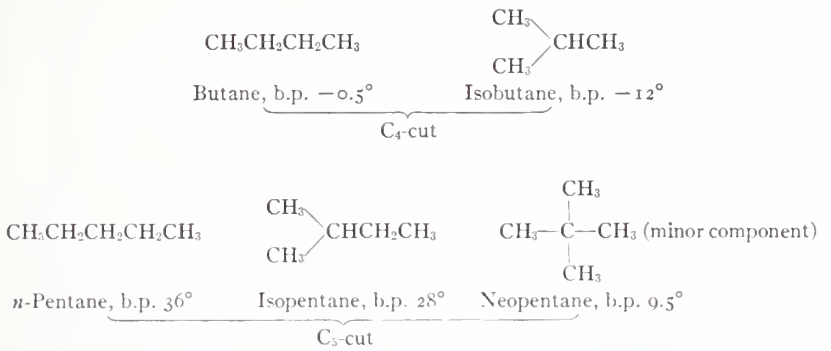
Natural gasoline

8.2 **Constituents.** — Natural gas, freed of natural gasoline, contains methane and decreasing amounts of C_2–C_4 homologs; gas from specific fields also contains either nitrogen or helium. Since the lower alkanes differ considerably in boiling point from one another and from nitrogen or helium, the components are separated efficiently by liquefication and fractional distillation under pressure at low temperature. Pure products produced in this way and their boiling points are: methane (−162°), ethane (−89°), propane (−42°), and helium (−269°). The hydrocarbons from this source are converted by selective cracking into unsaturated products useful in industrial syntheses. Two further useful fractions from natural gasoline that differ sufficiently from

Hydrocarbons from natural gasoline

Components separable

propane and from each other to be separable are called the C_4-cut and the C_5-cut. The chief components of each cut, or fraction, boil



C_4- and C_5-cuts of natural gasoline

too close to each other to be easily separable, but the mixtures serve adequately for uses which are to be described.

Hydrocarbon fractions from petroleum of boiling range higher than the C_5-cut are extremely complex mixtures. The major components are alkanes, straight-chain and branched. A second group of components, known in petroleum technology as naphthenes, are polyalkyl derivatives of cyclopentane and cyclohexane. A third group, described as aromatics, includes benzene, its methyl derivative toluene ($C_6H_5CH_3$), and other alkyl derivatives of benzene and the related naphthalene, $C_{10}H_8$. Petroleum also contains from 0.1 to 3% of naphthenic acid, a mixture of acids extractable with alkali. A few of countless components of the mixture have been isolated and identified as carboxylic acid derivatives of polyalkyl-substituted cyclopentanes or cyclohexanes. The naphthenic acid mixture thus contains carboxylic acid derivatives of the naphthene constituents. Aromatic nitrogen-containing compounds such as pyridine and quinoline are also present in traces (e.g., 0.008%) and are extractable with mineral acid. 8.3

Naphthenes and aromatics

Naphthenic acid

Fractional Distillation. — Separation of a mixture of liquids of different boiling points is done by fractional distillation in a still of which the most important part is a fractionating column. This column is a tube which is provided either with a series of perforated plates or with a porous packing, such as glass beads. A part of the vapor distilled from the boiling flask, or kettle, condenses and trickles down the column; the less volatile of two components condenses first. Fresh vapor from the flask forces its way up through the descending condensate with attendant interchange between heavy and light components; a more volatile part of the liquid vaporizes and a less volatile part of the vapor condenses. Equilibrations occur in all parts 8.4



FIG. 8.4b. — Packed laboratory column for analytical fractionation (about 50 theoretical plates); used for separation of light hydrocarbons with close boiling points. (Courtesy of the Shell Development Company.)

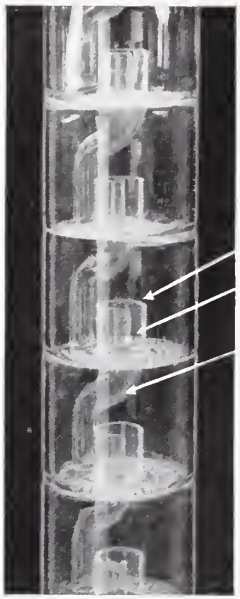


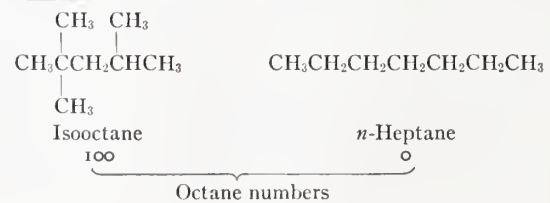
FIG. 8.4a. — Laboratory fractionating column with 37 perforated 31-cm. glass plates; efficiency: about 30 theoretical plates. (Courtesy of the Shell Development Company.)

of the column and the vapor that eventually passes into the condenser is enriched in the more volatile component, while the condensate that continually drops back into the flask is scrubbed of the volatile liquid and enriched in the less volatile one. Figure 8.4a shows a section of a perforated-plate column. The end of the drain pipe from one plate is placed close to the plate below it so that a liquid seal is formed and a depth of liquid maintained on the plate. The baffle directs flow of liquid through the weir into the drain pipe. Rising vapor forcing its way through the perforations rises through liquid condensate, and each plate thus affords abundant opportunity for equilibration. A column is rated according to the number of theoretical plates to which it is equivalent; a theoretical plate is defined as the equivalent of a single kettle-and-condenser combination with vapor and liquid in equilibrium, that is, one theoretically perfect distillation without a column. The greater the number of theoretical plates, the greater is the efficiency. A column performs in one operation what could be done, ideally and with unlimited time, in a sequence of a great many simple distillations.

MOTOR FUELS

8.5 Octane Rating. — The knock or ping heard when an automobile engine is accelerated too rapidly is a warning that conditions for efficient performance of the engine with the particular gasoline used have been exceeded. The knocking tendency of a given gasoline is expressed as the octane number, or the performance in a standard one-cylinder test engine in comparison with that of mixtures of two synthetic standard fuels. Isooctane (2,2,4-trimethylpentane), which deto-

Standards



nates only at high compression and was superior to any gasoline available in 1927 when the rating was introduced, was assigned the octane rating of 100, and *n*-heptane, which is particularly prone to knocking, was given the rating 0. The octane number of a fuel is the per cent of isooctane in a blend with *n*-heptane that has the same knocking characteristics as the fuel under examination. Investigation of pure synthetic hydrocarbons has shown that in the alkane series octane number decreases as the chain is lengthened and increases with chain branching. Alkenes have higher ratings than corresponding alkanes, and the octane number increases as the double bond is shifted to the center of the molecule. Cycloalkanes are less prone to knock than normal alkanes, and aromatic hydrocarbons have exceptionally high octane numbers.

Octane rating and structure

Engine efficiency increases with increased compression ratio, but so does knocking. Straight-run gasolines provided by distillation of petroleum have octane ratings as low as 20 (Michigan field) and, at best, no higher than 75, and hence engines of the nineteen twenties operating on such fuels had compression ratios of only about 4:1. However, technological discoveries have so increased octane ratings as to make possible engines of superior power and mileage of ratios of 8–10:1. 8.6

Diesel Fuel. — In Diesel engines the air alone is compressed, with the result that the temperature is increased to 480–540°. The fuel is injected almost at the end of the compression stroke and is spontaneously ignited. Diesel fuel need not be volatile, and generally consists of the fraction boiling between kerosene and lubricating oils. Owing to differences in engine construction, high-octane fuels are much less efficient than low ones. The ignition quality is expressed in terms of the cetane number, which refers to a mixture of cetane (n-$C_{16}H_{34}$, value = 100) and α-methylnaphthalene (value = 0); most automotive Diesel engines require a fuel of cetane number greater than 45; that is, the desirability of hydrocarbons is exactly reversed for the Diesel as compared with the ordinary engine. 8.7

Antiknock Compound. — The first major advance in improvement of motor fuels was discovery that knocking can be inhibited by addition of certain chemicals, the most important of which is tetraethyllead (TEL), developed by the American Thomas Midgley (1922). About 95% of all American gasolines contain tetraethyllead; gasolines leaded to an octane rating of 94 or more are known as premium gasolines. The commercial process consists in interaction of a sodium-lead alloy with ethyl chloride at moderate temperatures and pressures: 8.8

$$4\,PbNa + 4\,C_2H_5Cl \longrightarrow Pb(C_2H_5)_4 + 4\,NaCl + 3\,Pb$$

Tetraethyllead

The lead derivative is separated by steam distillation, and the lead sludge is smelted into pig lead.

Ethyl fluid; role of $BrCH_2CH_2Br$

Ethyl fluid contains not only tetraethyllead (63%), but also ethylene dibromide (26%), ethylene dichloride (9%), and a dye (2%). Ethylene dibromide is an essential constituent since it reacts with the lead oxide produced during combustion to form volatile lead bromide, which is swept from the cylinders in the exhaust gases. The manufacture of large amounts of ethylene dibromide presented a problem, since bromine was not available in sufficient quantity. The difficulty was solved by extraction of bromine from sea water, 7.5 tons of which contain one pound of bromine. An early process, operated on board the S.S. Ethyl, extracted bromine by adding aniline to chlorinated sea water and recovering bromine from the filtered precipitate of 2,4,6-tribromoaniline (6.18).

8.9 **Cracking.** — The perfection of practical processes for controlled pyrolytic decomposition, or cracking, of hydrocarbons boiling above 350° has had the immensely important result of more than doubling the amount of motor gasoline obtainable from petroleum. The large and relatively nonvolatile hydrocarbons of fractions otherwise used only as heavy fuel and for the building of roads, etc. can be broken down by thermal treatment into mixtures of smaller molecules having the desired volatility. The cracking of a fraction consisting of higher alkanes gives a mixture of alkanes and alkenes; since alkenes have advantageous octane ratings, cracked gasolines have superior antiknock characteristics. Several methods of cracking are employed in the industry: thermal cracking (500°, 30 atmosph.); moving bed, Houdry type catalyst: SiO_2–Al_2O_3–Cr_2O_3; fluid bed catalyst: SiO_2–Al_2O_3; thermal reforming: brief heating at high temperature and pressure; catalytic reforming: see 8.17. Cracked gasolines require protection to prevent oxidation, which initiates polymerization leading to gum formation. The oxidation is a chain reaction and can be inhibited by addition of a small amount of an antioxidant (phenols and aromatic amines).

Gasoline from kerosene

8.10 Studies of the pyrolysis of the gaseous hydrocarbons available from natural gas and natural gasoline have provided information concerning the reactions involved in cracking and have led to development of several synthetic intermediates of great technical importance.

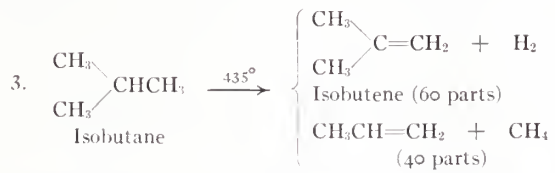
1. $CH_3CH_3 \xrightarrow{485°} CH_2{=}CH_2 + H_2$

2. $CH_3CH_2CH_3 \xrightarrow{460°}$ { $CH_3CH{=}CH_2 + H_2$ (45 parts); $CH_2{=}CH_2 + CH_4$ (55 parts) }

Ethane yields ethylene as an initial product of pyrolysis (1), and this alkene can be produced in high yield. The higher alkanes undergo both dehydrogenation and rupture, usually with formation of methane. Propane (2) affords both propylene, by dehydrogenation, and ethylene, by methane splitting. The branched-chain hydrocarbon isobutane (3) suffers both dehydrogenation and elimination of methane and gives isobutene as the chief product. Since isobutane is one

Production of ethylene and propylene

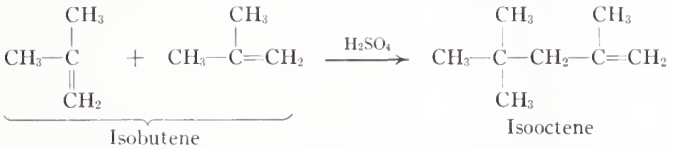
Isobutene by cracking



of the two major components of the C_4-cut from natural gasoline, cracking of this cut affords a mixture rich in isobutene.

Dimerization of Isobutene. — Treatment of isobutene with a catalytic amount of sulfuric or phosphoric acid causes one molecule to add to another to form the dimer, isooctene. Whereas the volatility of the

8.11



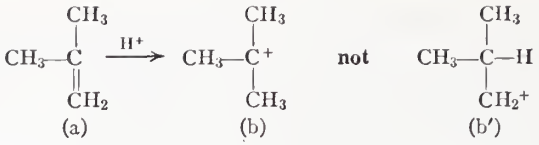
monomer isobutene limits its use as a motor fuel, the dimer has the proper volatility. The dimer has a high-octane number and is convertible by hydrogenation into isooctane. Since isobutene is a prominent component of the cracked C_4-cut, treatment of the whole cut gives a mixture rich in high-octane hydrocarbon. The sulfuric acid reaction, although actually a dimerization, is known to petroleum technologists as a "polymerization," and fuels made by this process and having octane numbers in the range 78–83 are known as "polymer gasolines."

"Polymer gasoline"

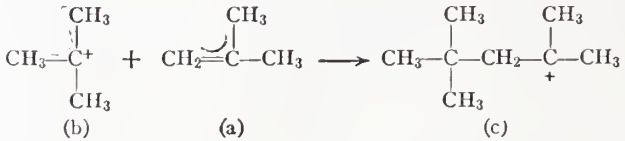
The acid-catalyzed dimerization of isobutene probably proceeds by the following reaction mechanism. A proton first attacks the terminal carbon of the double bond in (a) to give trimethylcarbonium ion (b), rather than the alternate ion (b′), because in (b) the charged carbon is partially stabilized by three electron-releasing methyl groups whereas in (b′) only one stabilizing group is available. The trimethylcarbonium ion (b) then attacks a second molecule of isobutene to give the dimeric ion (c) in which three alkyl groups stabilize the charged center. In the completing step, which balances the initiating step of attack by a proton, a terminal hydrogen is eliminated with the charge as a proton, with consequent appearance of a double bond and

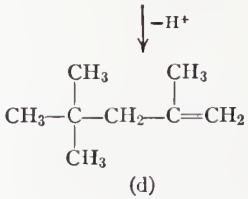
8.12

*



Mechanism of the dimerization



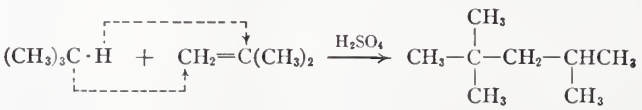


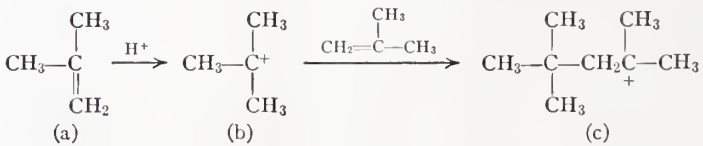
Isooctene (2,4,4-trimethylpentene-1)

formation of 2,4,4-trimethylpentene-1. Actually, about 20% of the product is the bond-isomer 2,4,4-trimethylpentene-2, resulting from elimination of hydrogen from (c) at position 3, rather than at position 1.

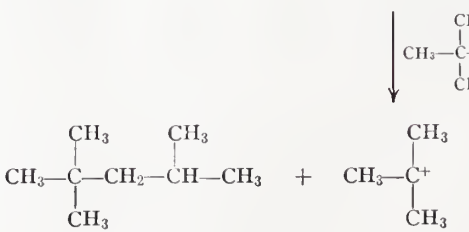
8.13 Alkylation. — A second reaction of considerable technological importance can be represented as an addition of an alkane to the double bond of an alkene but is usually described as the alkylation of an alkane. Alkylation of isobutane with isobutene gives isooctane, and

Isooctane by a second process





Mechanism in part the same as above

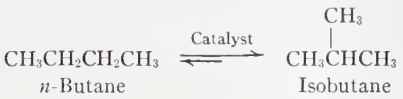


hence this important hydrocarbon is obtained in one step by partial cracking of the isobutane in the C_4-cut to produce a mixture of the two components, which is then treated with sulfuric acid. The reaction is very similar to the dimerization, and it likewise involves in the first step protonation of isobutene to form trimethylcarbonium ion (b) and, in the second step, addition of ion (b) to isobutene to form ion (c), identical with that above. However, if isobutane is present when ion (c) is formed, it gives up hydrogen to ion (c) and acquires the charge and thus produces a trimethylcarbonium ion (b), and the intermediate is thereby regenerated.

The reactions of dimerization and alkylation are not limited to the examples cited, but are generally applicable and are of considerable use in converting various components of cracking fractions into high-octane hydrocarbons. 8.14

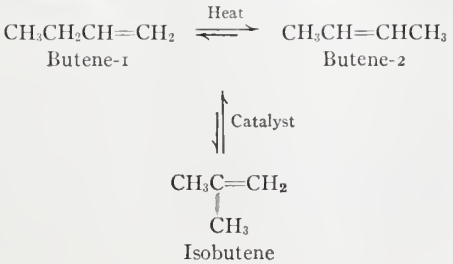
Isomerization. — When isobutane was recognized as a key chemical for the manufacture of high-octane fuel, methods were sought for increasing the proportion of isobutane beyond that of the original C_4-refinery cut from natural gasoline. Actually this cut contains more *n*-butane than isobutane. Thermal treatment proved of no avail, for at high temperatures (500–600°) *n*-butane is more stable than the branched isomer. It was found, however, that the hydrocarbons can be isomerized under the catalytic influence of aluminum chloride and that at 27° the equilibrium mixture contains 75–80% of isobutane. Thus the isobutane content of the C_4-cut can be enormously 8.15

Isobutane content can be increased



increased by equilibration in the presence of catalyst. The isomerization of *n*-butane to the branched isomer evidently involves migration of a methyl group.

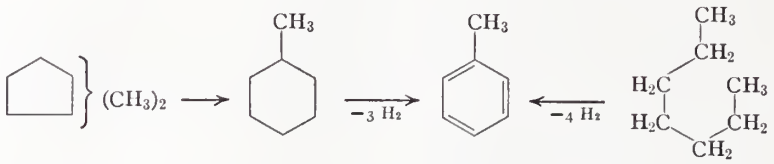
Alkenes also undergo isomerization, which can involve both migration of a double bond and migration of a methyl group. When heated in a quartz tube at 550°, butene-1 is isomerized to butene-2 to the extent of 87%. Partial isomerization of the butenes to iso- 8.16



Source of isobutene

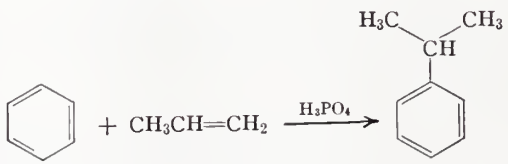
butene can be accomplished by alumina, aluminum sulfate, or phosphoric acid as catalyst.

8.17 **Aromatization.** — Toluene was formerly obtained only from coal tar, the production of which is geared to coke requirements, but this source is now inadequate. Large quantities of toluene are produced by the catalytic reforming of C_7-petroleum hydrocarbons, either by dehydrogenation of methylcyclohexane alone (b, molybdenum catalyst), by a combination process involving isomerization of dimethylcyclopentanes (a) to methylcyclohexane and dehydrogenation, or,



to a more limited extent, by cyclization of *n*-heptane (c). The latter reaction is done with a platinum catalyst modified by acidic components to have isomerizing as well as dehydrogenating properties. Usually these processes are applied to petroleum fractions containing hydrocarbons in the C_6–C_7 range, which yield both benzene and toluene, or to wider fractions (such as C_8–C_9) yielding also the xylenes, trimethyl-, and methylethylbenzenes. These mixtures are valuable as high-octane fuels, or may be treated for the recovery of particular aromatics or groups of aromatics for other uses such as chemical synthesis. Cumene (isopropylbenzene) is a valuable high-octane blending stock made by alkylation of benzene with propylene over a supported phosphoric acid catalyst.

Friedel-Crafts reaction



Cumene (b. p. 152°)

PETROCHEMICALS

8.18 Petrochemicals are organic compounds derived from petroleum by techniques of fractional distillation, cracking, isomerization, and chemical processing as required. Such chemicals are available on a huge scale at low cost, and they have acquired enormous importance as starting materials for synthesis and as intermediates to solvents, plastics, rubbers, and detergents. An example already cited (3.4) is the thermal chlorination of the C_5-cut from natural gasoline, sub-

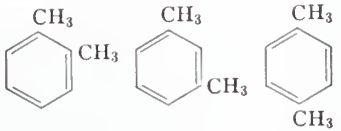
stantially a mixture of *n*-pentane and isopentane, to produce a mixture of chlorohydrocarbons useful both as a solvent and for conversion to an alcohol mixture which goes into the manufacture of lacquers. Products of selective cracking such as ethylene, propylene, and a butene mixture are convertible into ethyl alcohol, isopropyl alcohol, and *sec*-butyl alcohol, and the last two alcohols on oxidation give ketones. Acetylene, a key starting material for many important products, is made by cracking methane in an electric arc:

Chlorohydrocarbons, alcohols, ketones

$$2\ CH_4 \longrightarrow CH{\equiv}CH + 3\ H_2.$$

The list of useful petrochemicals includes certain key aromatics, particularly the three xylenes and products derived from them. The

8.19



ortho	*meta*	*para*
B. p. 144°	139°	138°
M. p. −25°	−48°	13°

Xylenes

three isomeric dimethylbenzenes have boiling points so close together as to be inseparable by fractionation in the stills used for distillation of coal-tar hydrocarbons, and separation of the components of coal-tar xylene by selective sulfonation (6.17) was far too costly for purposes of production. Development of the process of aromatization of petroleum opened the way to production of a mixture of the three xylenes on a scale far surpassing the production from coal tar. Since the individual hydrocarbons offered a much better potential use than the mixture, petroleum technologists worked on and developed a method for large-scale, low-cost production of substantially pure *o*-, *m*-, and *p*-xylene. The first step utilizes the extraordinarily efficient technique of fractional distillation that is one of the key factors in the success of the modern petroleum industry. Although the boiling point of *o*-xylene is only 5° higher than that of the *m*-isomer, *o*-xylene is produced in quantity by fractional distillation of the mixture. The *meta*- and *para*-isomers, of b.p. 139° and 138°, are not separable by known distillation techniques. However, the two isomers differ in melting point by no less than 61°; the more symmetrical *p*-isomer freezes at 13°, whereas *m*-xylene solidifies only at −48°. Thus the mixture remaining after removal of *o*-xylene by fractionation is separated by freezing out the *p*-isomer. By efficient processes of oxidation, the three xylenes afford the corresponding benzenedicarboxylic acids, which are petrochemicals of increasing importance in chemical technology.

Method of separation

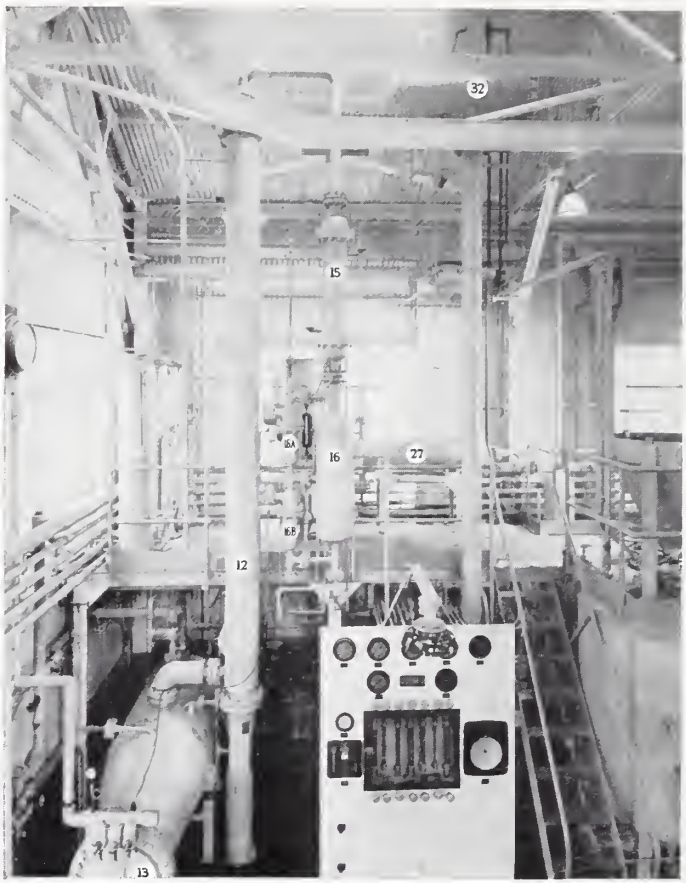
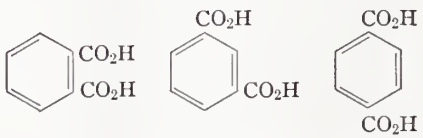


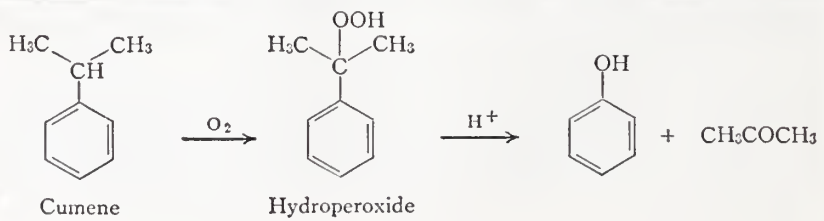
FIG. 8.19.— Batch distillation in a petrochemical pilot plant. Parts: kettle (13, below), fractionating column (12), condenser (15), phase separator (16). Control panel in right foreground. (Courtesy of the Shell Development Company.)

Corresponding diacids



8.20 Cumene, initially produced as a high-octane fuel blend, has found use also as starting material in a process for the joint manufacture of phenol and acetone. Air is blown into the liquid hydrocarbon in the

Production of phenol and acetone



presence of a trace of sodium hydroxide to inhibit premature decomposition of the sensitive hydroperoxide, which is formed by attack of the oxygen diradical, $\cdot\ddot{O}:\ddot{O}\cdot$, on the activated hydrogen of the isopropyl substituent. The hydroperoxide is then decomposed, by acid catalysis, to phenol and acetone.

SYNTHETIC FUELS FROM COAL

Bergius Process. — The production of fuels by destructive hydrogenation of coal was developed in Germany during World War I by Bergius. Coal probably is an elaborate network of carbon rings, which are cleaved during the process into fragments that are hydrogenated to open-chain and cyclic hydrocarbons. Powdered coal mixed with heavy tar (bottom of previous operation) is stirred with a tin or lead catalyst and hydrogen at high pressure and temperature (450–490°). The product is separated by distillation into gasoline (b.p. to 200°), gas oil (b.p. 200–300°), and a residue that is recycled with fresh coal. A typical gasoline fraction contains 74% alkanes, 22% aromatics, and 4% alkenes. Octane numbers of 75–80 are reported. 8.21

SUMMARY

Constituents. Methane, ethane, and propane separable from natural gas; natural gasoline affords propane, butanes, and a C_5-cut (mainly *n*-pentane and isopentane). Higher fractions are complex mixtures.

Aromatics: benzene, toluene, naphthalene.

Naphthenes (alkylated cycloalkanes). Naphthenic acid (mixture of carboxylic acids extracted by alkali).

Theory of fractional distillation.

Motor Fuels

Octane rating. Isooctane = 100, *n*-heptane = 0. Rating high for branched-chain alkanes, for alkenes, and aromatics.

Cetane rating. Requirements for a Diesel engine the reverse of those for a gasoline motor.

Antiknock compound: tetraethyllead (from PbNa + C_2H_5Cl). Ethyl fluid; function of ethylene dibromide.

Cracking. Conversion of otherwise practically waste high-boiling fractions into cracked gasoline of favorable octane rating (protection by antioxidants). Ethane ⟶ ethylene. Propane ⟶ propylene + ethylene. Isobutane (in the C_4-cut) ⟶ isobutene + propylene.

Acid-catalyzed dimerization of isobutene to isooctene ("polymer gasoline" of high octane rating). Ionic mechanism: initial attack by H^+ to give a carbonium ion.

Alkylation. Acid-catalyzed addition of isobutane to isobutene to give isooctane (described as the alkylation of an alkane with an alkene). Mechanism: attack by H^+ to give a carbonium ion, combination with isobutene, reaction with isobutane to reform the carbonium ion and give isooctane.

Isomerization (equilibrium). Butane ⟶ isobutane ($AlCl_3$ at 27°). Butene-1 ⟶ butene-2. Butene-1 and butene-2 ⟶ isobutene.

Aromatization. Catalytic dehydrogenation of methylcyclohexane to toluene. Toluene also from dimethylcyclopentane and from *n*-heptane. Xylenes from C_8-fraction. Cumene, $C_6H_5CH(CH_3)_2$.

Petrochemicals

Chlorination of the C_5-cut to produce solvents and derived alcohols. Alcohols from ethylene, propylene, and butenes available by cracking.

Xylene mixture produced by aromatization separable by fractional distillation followed by freezing out of the symmetrical *p*-isomer. Converted by oxidation to phthalic, isophthalic, and terephthalic acid.

Phenol and acetone from cumene through the hydroperoxide.

Synthetic Fuels from Coal

Bergius process. Hydrogenolysis of coal ⟶ gasoline (octane number 75–80).

PROBLEMS

1. Describe the steps by which the C_4-cut from natural gasoline is converted into high-octane "polymer gasoline" rich in isooctene.
2. How can the above process be varied to produce high-octane fuel rich in isooctene?
3. Suggest a mechanism for the reaction of cumene with oxygen to form a hydroperoxide.

CHAPTER 9

ACIDS AND BASES

CARBOXYLIC ACIDS AND PHENOLS

Acidity Constants. — In pure water the concentration of hydrogen ions, or $[H^+]$, is equal to that of hydroxide ions, $[OH^-]$, and both quantities have the numerical value 1×10^{-7}. The equilibrium constant for the slight dissociation of water, k, is 10^{-14}, that is, $[H^+] \times [OH^-] = 10^{-14}$. In a weakly acidic solution where $[H^+] = 10^{-6}$, the value of $[OH^-]$ is then $10^{-14}/10^{-6} = 10^{-8}$; in a strongly alkaline solution where $[OH^-] = 10^{-2}$, the value of $[H^+]$ is 10^{-12}. The exponential expression of ion concentrations is awkward and is now generally replaced by the logarithmic expression pH, defined by the equation 9.1

$$pH = -\log [H^+]$$

Thus a neutral solution has the pH 7, a slightly acidic one may have the pH 6, a slightly alkaline one the pH 8, a strongly acidic solution the pH 2, etc. In the same way, the dissociation constant of an acid, k_a, is translated into an acidity constant pK_a, defined as the negative logarithm of the dissociation constant, or

$$pK_a = -\log k_a$$ *Definition*

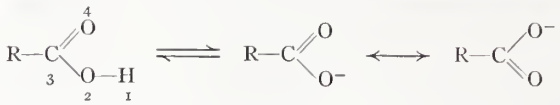
Acetic acid, a weak acid, has the acidic dissociation constant (k_a) of 1.75×10^{-5} and hence:

$$pK_a \text{ (acetic acid)} = -(-5 + 0.24) = 4.76$$ *Acetic acid*

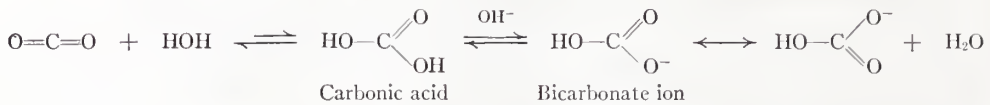
Carbonic acid is more weakly acidic than acetic acid; for separation of the first hydrogen as proton, $pK_{a_1} = 6.5$. Mineral acids are so highly dissociated that pK_a is not accurately measurable; presumably $pK = 1$ or less. *Carbonic acid*

Carboxylic Acids and Related Inorganic Acids. — In an earlier 9.2

chapter (2.30) the acidic character of the carboxylic acids was attributed to activation by a 3,4-double bond of the hydroxylic hydrogen



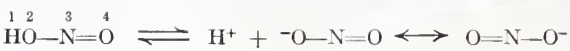
at position 1 and separation of this hydrogen as a proton under the driving force of resonance stabilization of the hybrid carboxylate ion formed. Carbonic acid can yield a similarly stabilized anion, but

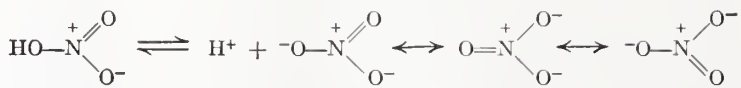


Carbonic acid weak because of instability

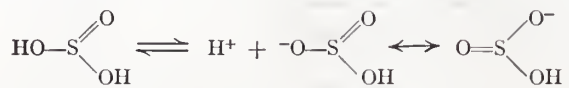
since this acid, unlike acetic acid, is unstable in water solution the concentration is so low that the substance is a weaker acid than acetic acid. The relationship is such that acetic acid liberates carbon dioxide from a solution of sodium bicarbonate. The same is true for all aliphatic and aromatic carboxylic acids, and hence a test with bicarbonate and observation that carbon dioxide gas is liberated is a useful means of recognizing a carboxylic acid. A solid acid insoluble in water not only liberates gas but goes into solution in the form of the ionic sodium salt, $RCOO^-Na^+$.

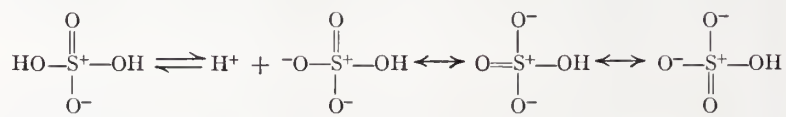
9.3 Nitrous, nitric, sulfurous, and sulfuric acid all have a hydroxylic hydrogen atom activated by a 3,4-double bond, and hence are analogous to acetic acid. The higher-valence acids (nitric, sulfuric) are more unsaturated than the lower-valence analogs and they are more strongly acidic.


Nitrous acid

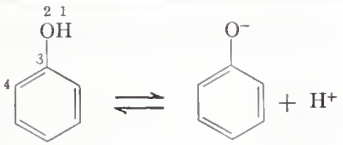

Nitric acid

Inorganic acids


Sulfurous acid


Sulfuric acid

Phenols. — Phenol has a phenolic hydrogen atom which can be described as activated by a 3,4-double bond of the ring or by the whole unsaturated phenyl group. This type of unsaturation does not produce as much activation as the potent carbonyl group of the car- 9.4



Phenol (m. p. 43°) Phenoxide ion
$pK_a = 10.0$

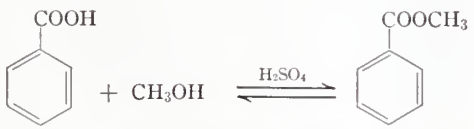
Very weakly acidic

boxylic acids and hence phenol is only weakly acidic, $pK_a = 10.0$. Thus a phenol that is insoluble in water dissolves in sodium hydroxide solution as does a carboxylic acid, but its phenolic character can be recognized from the fact that it does not dissolve in sodium bicarbonate solution. Since phenol is a weaker acid than carbonic acid, addition of carbon dioxide (e.g. as dry ice) to an aqueous solution of sodium phenoxide causes precipitation of free phenol.

Insoluble in bicarbonate

Neutral Derivatives of Acids. — Replacement of the hydroxylic hydrogen of a carboxylic acid by an alkyl group obviously eliminates the possibility for separation of a hydrogen ion and gives a neutral derivative, an ester. A typical esterification is illustrated in the photographs. A 50-g. batch of benzoic acid is charged into a round-bottomed flask, and 125 ml. of methanol and 15 ml. of concentrated sulfuric acid are added. The acid dissolves readily when the mixture is 9.5

Esters



Benzoic acid
M. p. 122°

Methyl benzoate
B. p. 199°

Fischer esterification



(a)



(b)



(c)

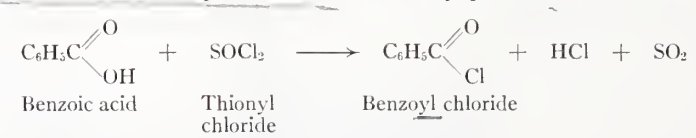
Heating under a reflux condenser

warmed, and the solution of acid, alcohol, and catalyst is then refluxed on the steam bath. This is done by fitting the reaction flask with a vertically mounted Liebig condenser cooled by water running through the jacket. Methanol (b.p. 65°) steadily volatilizes, but the vapor is condensed in the cooled condenser tube and returned to the flask. In this way maximum heat can be applied for as long as desired without loss of a volatile solvent or reactant. After refluxing for two hours the mixture is cooled, poured into a separatory funnel, diluted with water, and extracted with ether. After the ether-water mixture has been shaken and the layers let separate, the lower layer containing most of the methanol and sulfuric acid is run off, and the ethereal solution is washed with water, that is, water is added, the mixture shaken thoroughly, and the water layer drawn off and discarded. The ethereal solution is then extracted with 5% sodium bicarbonate solution and the bicarbonate layer drawn off and saved. The reason for this operation is that the reaction is one of equilibrium and a small amount of unesterified benzoic acid remains as a contaminant in the product. Washing with bicarbonate removes this substance. In the experiment illustrated the bicarbonate solution was heated on the steam bath to remove dissolved ether, acidified, and allowed to cool, when 1.4 g. of benzoic acid crystallized and was recovered (c). The methyl benzoate remaining in the neutral ethereal solution was isolated by drying the ethereal solution and evaporating the ether; the yield of liquid ester was 51.6 g. (c).

Separation of acid from ester by bicarbonate extraction from ether

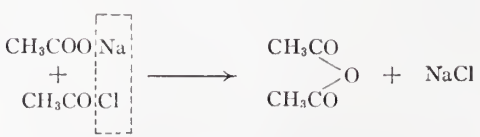
9.6 Carboxylic acids are also convertible into acid chlorides and anhydrides, which, like esters lack an ionizable hydrogen atom and are neutral derivatives. Acid chlorides are obtainable readily by reaction of an acid with thionyl chloride. The by-products are both gases,

Preparation of acid chlorides



hydrogen chloride and sulfur dioxide, and are hence readily removed from the reaction product, for example, benzoyl chloride. Acetic anhydride was formerly manufactured by reaction of sodium acetate with acetyl chloride, but a modern process utilizes the highly reactive

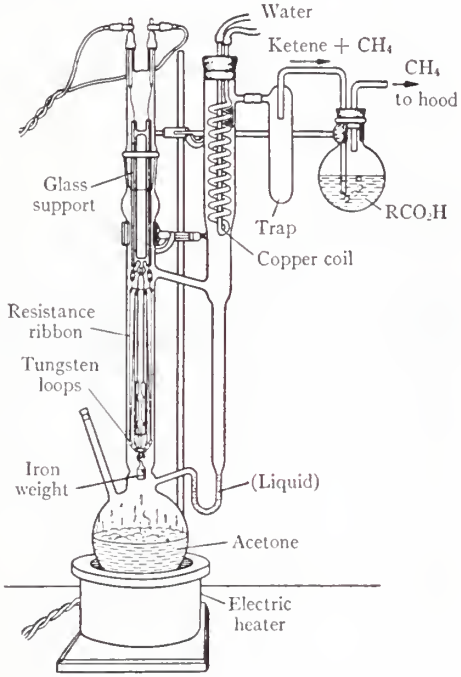
Anhydrides



reagent ketene, produced by the cracking of acetone. Methane results from the pyrolysis by elimination of the methyl group along

$$H(CH_3)CH_2{-}C{=}O \xrightarrow{700\text{–}750^\circ} \underbrace{CH_2{=}C{=}O}_{\text{Ketene (b.p.} -56^\circ)} + CH_4$$

with an activated hydrogen in the α-position. Ketene can be prepared in the laboratory in the generator illustrated. Vapor of refluxing acetone comes in contact with a glowing grid of resistance wire and undergoes cracking; unchanged acetone is condensed and returned to the boiling flask, and the ketene evolved in the gas stream along with methane is absorbed directly by a liquid reagent or in a solution.



Ketene Generator

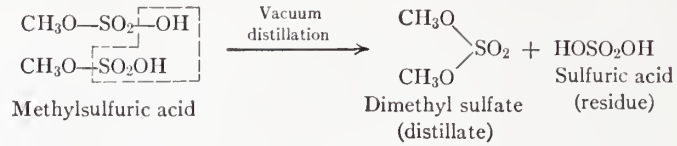
Ketene, which has a carbonyl group twinned with an ethylenic double bond, adds acetic acid to form acetic anhydride, probably by addition to the carbonyl group and 2,4-migration of the enolic hydrogen atom (3.23).

$$CH_3COOH + CH_2{=}C{=}O \longrightarrow \left[CH_2{=}C(OH){-}O{-}CH_3C{=}O\right] \longrightarrow CH_3C(=O){-}O{-}CH_3C{=}O$$

Acetic anhydride from ketene

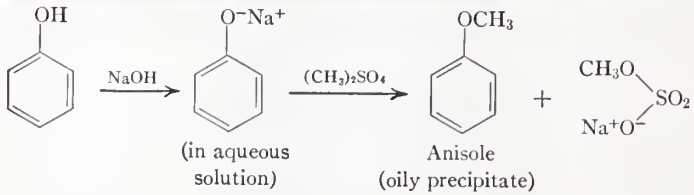
Phenol Methyl Ethers. — The methyl derivative of phenol is not an ester but an ether, and it cannot be made by Fischer esterification. 9.7

The best method of preparation utilizes a reagent which, like methyl benzoate, is a neutral ester, namely, dimethyl sulfate, the dimethyl ester of sulfuric acid. It is a liquid made by vacuum distillation of



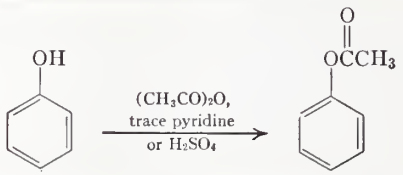
the monomethyl ester, methylsulfuric acid, as shown in the equation. Methylation of phenol is accomplished by dissolving the substance in aqueous alkali to produce a solution of sodium phenoxide and adding dimethyl sulfate gradually with vigorous stirring to give the

Methylation of phenol



water-insoluble reagent full opportunity to react. As the neutral methyl ether (anisole) forms, it separates as an oil; dimethyl sulfate is converted into the sodium salt of methylsulfuric acid. Phenol is acetylated by warming it with acetic anhydride and either a basic

Acetylation of phenol



catalyst such as pyridine or an acidic one such as sulfuric acid. The product, phenyl acetate, is neutral.

9.8 Inductive Effect in Acids. — In the series of normal acids from acetic (C_2) to caproic (C_6), the acidity constants are all essentially

TABLE 9.8

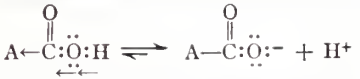
Acidic Strength

Acidity constants

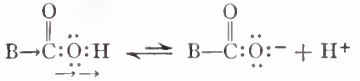
Acid	*Formula*	pK_a	
Formic	HCOOH	3.77	(stronger than the homologs)
Acetic	CH_3COOH	4.76	
Propionic	CH_3CH_2COOH	4.88	
n-Butyric	$CH_3CH_2CH_2COOH$	4.82	(all about the same)
n-Valeric	$CH_3CH_2CH_2CH_2COOH$	4.81	
n-Caproic	$CH_3CH_2CH_2CH_2CH_2COOH$	4.85	

the same, $pK_a = 4.8–4.9$. Formic acid, the only member of the series which has a hydrogen atom rather than an alkyl group joined to

carboxyl, is distinctly more acidic than the homologs of the type RCO_2H. An interpretation of the effect of the group A on the ionization of the acid A—COOH advanced by G. N. Lewis in 1923 was the first recognition of what is now known as an inductive effect. If A is electron-attracting, the inductive displacement of the electron pair between carbon and A in the direction of A will cause secondary displacements of electrons of the C:O and O:H bonds and hence facilitate separation of the hydroxylic hydrogen as a proton:



A group B that repels electrons will produce a displacement in the opposite direction and decrease the extent of ionization. Since acetic



Acidic strength related to electron-attracting or electron-releasing character

acid is a weaker acid than formic, the methyl group has less attraction for electrons than a hydrogen atom, or is relatively electron-repelling: $CH_3{\rightarrow}COOH$. The conclusion agrees with that inferred from the effect of methyl substituents on the rate of bromination of ethylenes (3.14). The higher normal homologs are so close to acetic acid in pK_a that any difference in electron release between methyl, ethyl, and higher groups must be so slight as to be obscured in the transmissal of the inductive effect through two covalent links.

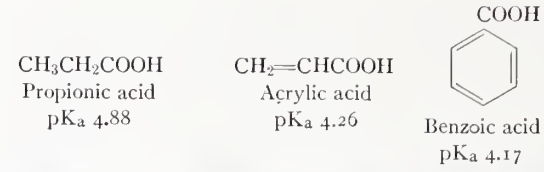
Substitution of one of the α-hydrogen atoms of acetic acid by chlorine greatly increases the acidic strength: $CH_2ClCOOH$, pK_a 2.81. Chlorine, therefore, is strongly electron-attracting and produces displacements of the type $Cl{\leftarrow}C(=O){\leftarrow}O{\leftarrow}H$. That the inductive effect of a substituent decreases rapidly with increasing distance from the hydroxylic hydrogen is shown by comparison of α- and β-chloropropionic acid. The α-chloro acid is much more acidic than the parent acid, whereas the β-chloro isomer is only slightly more

9.9

Halogen is electron-attracting

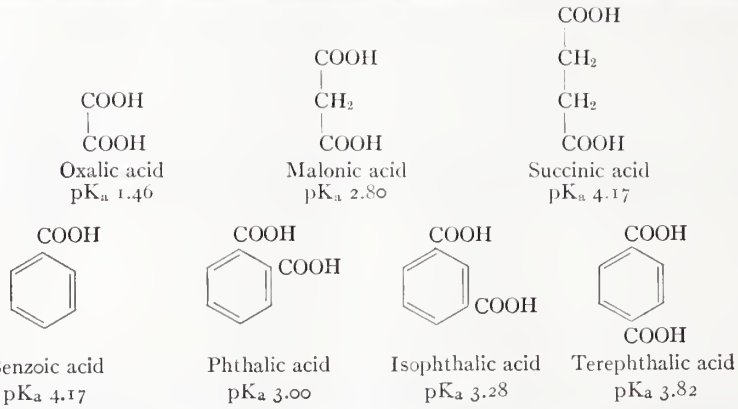
CH_3CH_2COOH	$CH_3CHClCOOH$	$ClCH_2CH_2COOH$
Propionic acid	α-Chloropropionic acid	β-Chloropropionic acid
pK_a 4.88	pK_a 2.80	pK_a 4.08

acidic. Substitution in acetic acid of one, two, and three α-chlorine atoms produces progressive shifts to greater acidic strength, and trichloroacetic acid (pK_a 0.08) almost reaches the acidity of mineral acids. Since acrylic acid is a somewhat stronger acid than propionic acid, the vinyl group ($CH_2{=}CH—$) is electron-attracting. Benzoic acid is comparable to acrylic acid in both structure and acidity; it is slightly more strongly acidic than acetic acid.



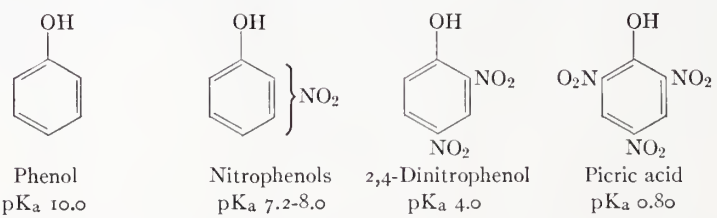
9.10 Striking inductive effects are observable in both aliphatic and aromatic dibasic acids. The carboxyl group is strongly electron-attracting, and one carboxyl joined to another (oxalic) greatly increases the acidic strength. The effect is still strong if the two carboxyls are separated by one methylene group (malonic), and nearly disappears if there are two intervening carbon atoms. The effect of one carboxyl on another is transmitted more efficiently along carbon atoms of the resonant benzene ring.

One COOH close to another increases its acidic strength

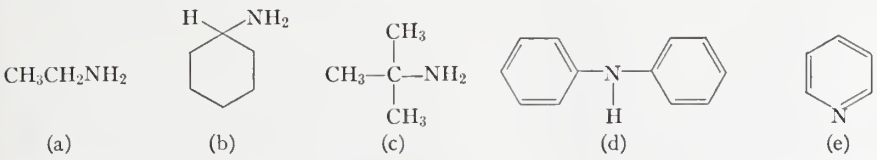


9.11 **Inductive Effect in Phenols.** — The most significant effect of substituents on the dissociation of phenols is that of the positively polarized, strongly electron-attracting nitro group. A single nitro group in the *o*-, *m*-, or *p*-position increases acidity to the extent of reducing the pK_a of phenol from 10 to 7.2–8.0; the positive nitro group displaces electrons in its direction and so favors separation of the hydroxylic hydrogen with a positive charge. A second and third nitro group accentuates the effect of the first, and the pK_a values of 2,4-dinitrophenol and of picric acid show evidence of the cumulative effect. Picric acid, which is 2,4,6-trinitrophenol, approaches the mineral acids in acidic strength (pK_a = 0.8).

NO_2-Substitution increases acidic strength



Types; Preparation. — Amines are derivatives of ammonia in which one, two, or three of the hydrogen atoms have been replaced by alkyl or aryl groups, and they are designated primary, secondary, or tertiary according to the number of alkyl groups attached to nitrogen. Thus ethylamine (a), cyclohexylamine (b), and *t*-butylamine (c) 9.12



(a) (b) (c) (d) (e)

are all primary amines of the type RNH_2, for in each case only one hydrogen atom of ammonia is replaced by an alkyl group; it is inconsequential to the classification whether the alkyl group is primary (a), secondary (b), or tertiary (c). Diphenylamine (d) is a secondary amine, since two hydrogens of the ammonia molecule are replaced by phenyl groups. Pyridine (e) is a tertiary amine because all three hydrogens of ammonia are replaced by bonds to carbon atoms.

Primary, secondary, and tertiary

Primary aliphatic amines can be prepared by the action of ammonia on an alkyl halide, a reaction described as an amination. Amination of ethyl bromide involves an initial addition of this halide to trivalent nitrogen to form a pentavalent ammonium salt, ethylammonium bromide (1), which on treatment with alkali affords free 9.13

Prepared by amination of alkyl halides

1. $CH_3CH_2Br + NH_3 \longrightarrow CH_3CH_2N^+H_3Br^- \xrightarrow{NaOH} CH_3CH_2NH_2$

ethylamine. A complication is that the ethylammonium bromide as it is formed enters into equilibrium with ammonia still present with liberation of ethylamine (2). The primary amine then competes with ammonia for the alkyl halide and yields some of the secondary amine salt (3). However, a simple expedient for suppression of the unwanted

2. $CH_3CH_2N^+H_3Br^- + NH_3 \rightleftharpoons CH_3CH_2NH_2 + NH_4^+Br^-$

3. $CH_3CH_2NH_2 + CH_3CH_2Br \longrightarrow (CH_3CH_2)_2N^+H_2Br^-$

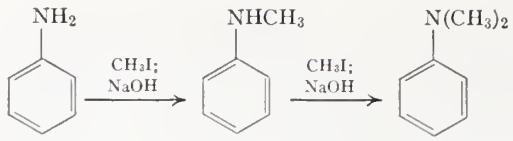
secondary amine is to use so large an excess of ammonia that the competitive reaction (3) has little chance of occurring. An example is the amination of α-bromopropionic acid (4).

4. $CH_3CHCO_2H \xrightarrow[65\text{-}70\%]{NH_3\ (70\ \text{equivalents})} CH_3CHCO_2H$
(Br) → (NH2); Alanine

Use of excess ammonia

Secondary amines can be made by alkylation of primary amines, and tertiary amines by repetition of the process (5). These reactions 9.14

5.



N-Methylaniline N,N-Dimethylaniline

are not easily controlled to just the desired stage of alkylation, and the reaction products require extensive purification. A tertiary amine is not a terminal product of alkylation, since an alkyl halide can add to the trivalent nitrogen to give a pentavalent nitrogen salt, for example, tetramethylammonium bromide (6). Salts of the type $R_4N^+Br^-$ are called quaternary ammonium bromides, since they are derivatives

Quaternary ammonium salt

6. $(CH_3)_3N + CH_3Br \longrightarrow (CH_3)_4N^+Br^-$
Tetramethylammonium bromide

of ammonium bromide in which all four hydrogens are replaced by alkyl groups.

9.15 Primary aromatic amines are readily available by reduction of the corresponding nitro compounds resulting from nitration. Aliphatic amines are obtainable by similar reduction of unsaturated nitrogen compounds of various types. Nitriles, $RC{\equiv}N$, yield primary amines, RCH_2NH_2, on hydrogenation. Thus propionitrile, from ethyl

Reduction of unsaturated nitrogen compounds

7. $CH_3CH_2C{\equiv}N \xrightarrow{2\ H_2\ (Pt)} CH_3CH_2CH_2NH_2$
Propionitrile *n*-Propylamine

bromide and potassium cyanide, yields *n*-propylamine on catalytic hydrogenation.

9.16 **Basic Properties.** — Amines, like ammonia, give an alkaline reaction in aqueous solution and form salts with acids. The essential process is combination of a proton with nitrogen by utilization of the unshared pair of electrons (a). The alkaline reaction of an aqueous

(a) $(CH_3)_3N: + H^+ \longrightarrow (CH_3)_3\overset{+}{N}:H$

(b) $(CH_3)_3N: + H^+OH^- \rightleftharpoons (CH_3)_3\overset{+}{N}:H + OH^-$

solution of an amine is due to excess hydroxide ion concentration following withdrawal of hydrogen ions as in (a), and the overall result can be represented as in (b). The basic dissociation constant of an amine, k_b, is the product of the concentrations of the ammonium and hydroxide ions divided by the total concentration of nonionized material:

$$k_b = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2]}$$

Basic strength, like acidic strength, is conveniently expressed as the negative logarithm of the dissociation constant, thus $pK_b = -\log k_b$.

A strong base has a low pK_b value (NaOH, pK_b about 0), and a weak one has a value approaching the limit $pK_b = 14$. Methylamine and

NH_3	4.7	pK_b values
CH_3NH_2	3.4	
$(CH_3)_2NH$	3.2	
$(CH_3)_3N$	4.2	
$CH_3CH_2NH_2$	3.3	

ethylamine are stronger bases than ammonia by 1.3–1.4 pK_b units. This effect of alkyl substitution appears attributable to the electron release of the methyl or ethyl group, which increases its affinity for a proton. The relationship of the secondary and tertiary amines seems to be associated with steric effects.

Ammonium hydroxide, $NH_4^+OH^-$, has little stability and exists 9.17
in water solution mainly as the decomposition products, ammonia and water. The instability of the hydroxide accounts for the fact that it is a weak base. The same is true of the hydrates of primary, secondary, and tertiary amines, but the situation is entirely different when all four hydrogens of the ammonium ion are replaced by alkyl groups. Addition of silver hydroxide to an aqueous solution of tetramethylammonium iodide and removal of the precipitate of silver

$$(CH_3)_4N^+I^- + AgOH \longrightarrow \underset{\substack{\text{Tetramethyl}\\\text{ammonium}\\\text{hydroxide}}}{(CH_3)_4N^+OH^-} + AgI$$

Quaternary ammonium hydroxides are stable and strongly basic

iodide gives a solution of tetramethylammonium hydroxide, which can be isolated by evaporation of the solution. With no hydrogen available for separation with the hydroxyl group as water, this quaternary ammonium hydroxide is stable in water and, probably because of its ability to exist in water solution at high concentration, it is a strong base, comparable to sodium and potassium hydroxide.

Any unsaturated group joined to nitrogen decreases the basic 9.18
strength and, since the benzene ring is unsaturated, aniline has only weakly basic properties (pK_b 9.3) as compared with methylamine (pK_b 3.4). The basicity, though weak, is sufficient for formation of salts with strong acids; and aniline, like water-insoluble aliphatic amines, is soluble in dilute hydrochloric acid. Amines of both classes are thus recognizable by their ability to form water-soluble, ether-insoluble salts with hydrochloric acid. If an amine is of low enough molecular weight to be soluble in water, it is also volatile enough to be recognizable by a fishy, ammonia-like odor, which disappears on neutralization with hydrochloric acid. Odorless amines are insoluble in water but soluble in dilute hydrochloric acid.

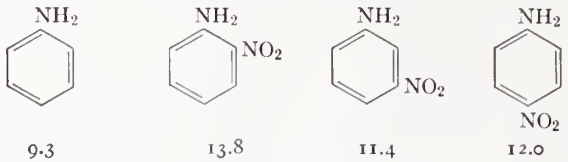
Aniline a weak base

Salt formation

Nitro groups in the benzene ring decrease the basic strength of an 9.19

amine just as they increase the acidic strength of a phenol. The pK_b values show that all three nitroanilines are weaker bases than aniline.

Inductive effect of nitro group



9.3 13.8 11.4 12.0

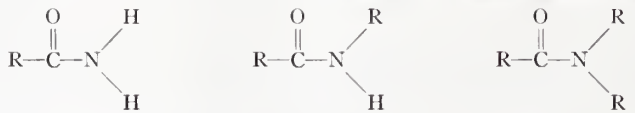
pK_b values

The effect of a nitro group at any position in the ring can be attributed to the inductive effect; the positively polarized nitro group induces a drift of electrons in the sense of withdrawal from the ring and from the amino nitrogen atom, and hence affinity of nitrogen for a proton is decreased. The difference in pK_b of the three isomers is reflected in the behavior of their salts on dilution. They all form colorless salts with concentrated hydrochloric acid, and these are hydrolyzed on dilution with moderate amounts of water to yellow, water-insoluble bases. When equal amounts of the salts are diluted in the same way, the *ortho* isomer is precipitated most readily, the *para* compound separates next, and *m*-nitroaniline separates only on more extensive dilution.

AMIDES AND IMIDES

9.20 Amides are compounds having a carbonyl group linked to nitrogen in any of the arrangements formulated. The unsaturated car-

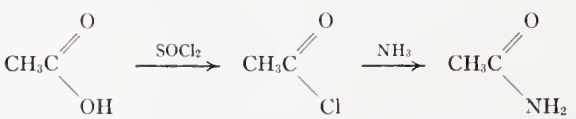
Amide types



bonyl group is an acid-forming group and balances the base-forming nitrogen, and hence amides are neutral substances inert to hydrochloric acid and no more soluble in mineral acid than in water. Hence they are neutral derivatives of amines, much as esters are neutral derivatives of acids. Like esters, they are hydrolyzable.

9.21 Amides of type (a) are made from acids by conversion to the acid chlorides and reaction of the latter derivatives with ammonia. Thus acetic acid affords acetamide, a crystalline, neutral solid. On

Amide from an acid chloride



Acetamide (m.p. 82°)

boiling with water containing hydrochloric acid or alkali as catalyst, and subsequent neutralization, acetamide is hydrolyzed to acetic acid and ammonia. Acetamide is also an intermediate in the hydrolysis

Amide by partial hydrolysis of a nitrile

$$\underset{\text{Acetonitrile}}{CH_3C{\equiv}N} \xrightarrow{H_2O} CH_3CONH_2 \xrightarrow{H_2O} CH_3COOH$$

of acetonitrile to acetic acid (3.26). The most common amides of types (b) and (c) are those obtainable in high yield by the acetylation of primary or secondary amines by reaction with acetic anhydride or acetyl chloride to effect replacement of an amino hydrogen by an acetyl group. Although a primary amine has two replaceable hydrogen

Acetyl amines

$$\underset{\text{Primary amine}}{(CH_3)_2CHCH_2NH_2} \xrightarrow{(CH_3CO)_2O} \underset{\substack{\text{Acetylisobutylamine}\\(\text{m.p. } 107^\circ)}}{(CH_3)_2CHCH_2NHCOCH_3} + CH_3CO_2H$$

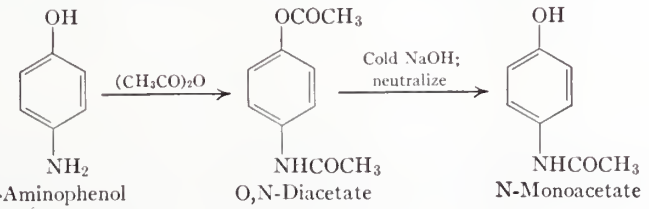
$$\underset{\text{Secondary amine}}{\begin{matrix}(CH_3)_2CH\\ \diagdown\\ \quad NH\\ \diagup\\ (CH_3)_2CH\end{matrix}} \xrightarrow{CH_3COCl} \underset{\substack{\text{Acetyldiisopropylamine}\\(\text{liq., b.p. } 222\text{–}225^\circ)}}{\begin{matrix}(CH_3)_2CH\\ \diagdown\\ \quad NCOCH_3\\ \diagup\\ (CH_3)_2CH\end{matrix}} + HCl$$

atoms, diacetyl compounds are rarely encountered. The monoacetyl derivatives of primary and secondary amines are useful for characterization and identification, particularly since acetylation often converts a liquid amine into a solid product.

Although amides can be hydrolyzed, the reaction proceeds only under conditions considerably more drastic than the conditions required for hydrolysis of esters. The difference is well illustrated by the behavior of the O,N-diacetate resulting from acetylation of

9.22

Selective hydrolysis



p-aminophenol. When shaken with cold, dilute sodium hydroxide, the diacetate crystals slowly dissolve as the phenolic hydroxyl group is liberated. Even though excess alkali is present, the N-acetyl group remains unattacked, and on acidification the N-monoacetate precipitates in high yield. The O-acetyl group thus selectively hydrolyzed by cold alkali contains an ester linkage, and the more resistant N-acetyl group an amide linkage.

Urea is an amide of a special type, for it contains two amino

9.23

groups and only one acid-forming carbonyl group. Hence urea is more basic than ordinary amides and forms salts with mineral acids.

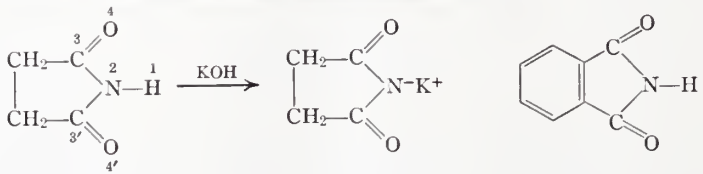


Urea — Urea nitrate

Urea, a metabolite

Urea is a product of metabolism of proteins in the animal organism, and the normal individual excretes in the urine 28–30 g. of urea per day. For isolation of urea, urine is evaporated to a thick syrup, which is extracted with hot ethanol. The ethanol is evaporated from the extract and the residue treated with nitric acid to form urea nitrate, which can be obtained as colorless crystals and converted into urea by neutralization with barium carbonate.

9.24 An imide has two carbonyl groups both linked to nitrogen, as shown in the formulas of succinimide and phthalimide. The hydrogen on



Succinimide pKa 10.5 — Phthalimide pKa 8.3

nitrogen is activated by double bonds in the 3,4- and 3′,4′-positions and is thus able to separate as a proton. Succinimide and phthalimide are weak acids soluble in alkali because of salt formation.

9.25 **Sulfonamides.** — The product of the reaction of benzoyl chloride with aniline, benzanilide (I), is a neutral substance insoluble in hy-

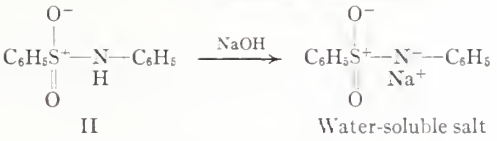
$$C_6H_5COCl + H_2NC_6H_5 \longrightarrow \underset{\text{Benzanilide (I)}}{C_6H_5CONHC_6H_5} + HCl$$

drochloric acid or in alkali, since the acid-forming carbonyl group balances the inherent basic character of nitrogen. The analogous product II from benzenesulfonyl chloride and aniline, however, is soluble in dilute alkali. The difference is attributable to the fact that

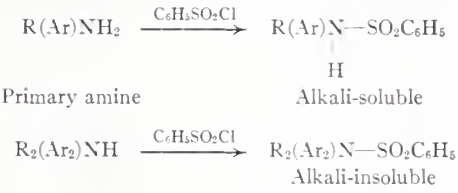
$$\underset{\text{Benzenesulfonyl chloride}}{C_6H_5SO_2Cl} + H_2NC_6H_5 \longrightarrow \underset{\text{II}}{C_6H_5SO_2NHC_6H_5} + HCl$$

the reagent, $C_6H_5SO_2Cl$, is the chloride of benzenesulfonic acid, $C_6H_5SO_2OH$, which, like sulfuric acid, is much more strongly acidic than benzoic acid. The sulfone group $—SO_2—$ is thus so powerfully acid-forming as to overshadow the basic nature of nitrogen. The

character of the group is attributable to the inductive effect of the unsaturated and positively charged sulfur atom. The hydrogen atom



attached to nitrogen is induced to separate as a proton; hence the sulfonamide II, which is insoluble in water, is brought into solution by addition of dilute alkali. A practical application of the facts cited is named after the German discoverer, Otto Hinsberg: the **Hinsberg test** for distinguishing between primary and secondary amines. All primary amines, whether they are aliphatic, aromatic, or of mixed type, react with benzenesulfonyl chloride to give alkali-soluble benzenesulfonyl derivatives (a). Secondary amines (b) give Hinsberg deriva-

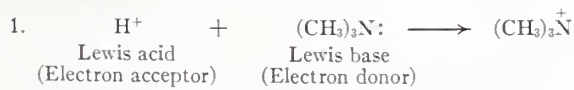


tives in which the nitrogen atom has no hydrogen available for salt-formation, and which therefore are insoluble in alkali. A tertiary amine is differentiated from the other two types because, with no nitrogen-bound hydrogen, it cannot form a Hinsberg derivative. Hence a basic, nitrogen-containing compound giving an alkali-soluble Hinsberg derivative is recognized as a primary amine; one giving an alkali-insoluble derivative is secondary; one that fails to react is a tertiary amine.

LEWIS ACIDS AND BASES

G. N. Lewis introduced a useful concept in which an acid is defined as an electron acceptor and a base as an electron donor. In the combination of hydrogen ion with an amine, the former functions as a Lewis acid and the amine, with its pair of unshared electrons, functions as a Lewis base (1). Trimethylboron carries no positive charge, as a

9.26



proton does, but since it possesses only six electrons it tends to acquire two more to form an octet, and hence it is an electron acceptor, or Lewis acid, as evident from its reaction with trimethylamine (2).

Trimethylboron



Lewis acid Lewis base

The reaction of neutralization can be regarded as combination of a proton, as a Lewis acid, with hydroxide ion, a Lewis base.



Lewis acid Lewis base Water

9.27 Oxygen-containing compounds are not so strongly basic as amines but nevertheless have basic properties understandable from the Lewis concept. Ethers are basic enough to combine with strong mineral acids to form oxonium salts, $[R_2OH]^+X^-$, comparable to ammonium salts, $[NH_4]^+X^-$. Thus dimethyl ether combines with hydrogen chloride by attachment of a proton to oxygen by one of the unshared electron pairs to produce a cation that is bound to the chloride ion by electrostatic forces. The salt exists only in a strongly acidic medium

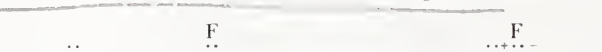
Basic properties of ethers



Lewis base Oxonium salt

and is decomposed to the components by water. Ethers dissolve in cold concentrated sulfuric acid owing to formation of oxonium salts, $[R_2OH]^+OSO_2OH^-$, and they are thereby readily distinguishable and separable from alkanes and alkyl halides. If the sulfuric acid solution of the oxonium salt is diluted carefully by pouring it slowly on ice, the ether can be liberated in unchanged condition. Boron fluoride is a Lewis acid because the boron atom, with an original sextet of electrons, can form an octet by accepting electrons; ether serves as an electron donor, or base, and the two reactants form a stable complex, boron fluoride etherate, which distils without decomposition. Boron fluoride,

Boron fluoride etherate



Lewis base Lewis acid Boron fluoride etherate (b.p. 126°)

a gas, is an excellent catalyst for esterification and acylation and is conveniently employed as the etherate.

SUMMARY

Acids and Phenols

Acidity expressed as pH = $-\log [H^+]$. Neutral solution, pH 7; strongly acidic, pH 1–2; strongly alkaline, pH 11–12. Dissociation of acetic acid: classical constant, $k_a = 1.75 \times 10^{-5}$; acidity constant, $pK_a = -\log k_a = 4.76$. Carbonic acid, $pK_a = 6.5$ (first proton).

Acidity of RCOOH due to activation of H by 3,4-double bond and separation of H^+ to form resonance-stabilized carboxylate ion. Carbonic acid weaker because of instability; RCOOH liberates CO_2 from carbonates and bicarbonates. Other acids with OH on an unsaturated atom: HONO, $HONO_2$, HO(SO)OH, $HOSO_2OH$.

Phenol: H of OH activated (weakly) by unsaturated ring; pK_a = 10.0. Phenol soluble in NaOH but not in $NaHCO_3$ solution (is a weaker acid than carbonic).

Neutral derivatives. Fischer esterification of benzoic acid (solid) to form methyl benzoate (liquid): reflux in excess methanol with H_2SO_4 as catalyst; recover unreacted $C_6H_5CO_2H$ by extraction with $NaHCO_3$ from an ether solution; collection of the ester from the neutral fraction.

Benzoic acid + thionyl chloride ($SOCl_2$) ⟶ benzoyl chloride. Acetic anhydride: (1) $CH_3COCl + CH_3COONa$. (2) Acetone by cracking ⟶ $CH_2{=}C{=}O$ (ketene), and addition of acetic acid to ketene.

Phenol methyl ether (anisole) by reaction of phenol in alkaline solution with dimethyl sulfate (prepared by vacuum distillation of methylsulfuric acid). Acetylation of phenol with acetic anhydride catalyzed by either pyridine or H_2SO_4.

Inductive effect of substituents on acidic strength (G. N. Lewis). An electron-attracting group A in A—COOH induces displacement of electrons away from the hydroxylic H and facilitates its separation as a proton. An electron-releasing group B (B—COOH) decreases ionization. Since CH_3COOH is weaker acid than HCOOH, CH_3 is electron-repelling as compared with H (agrees with evidence from bromination of alkenes). α-Chloro substitution greatly increases acidic strength, hence Cl is strongly electron-attracting. Inductive effect of Cl decreases in β-position.

The vinyl group, $CH_2{=}CH—$, is electron-attracting, since acrylic acid, $CH_2{=}CHCO_2H$, has the pK_a 4.26, while for $CH_3CH_2CO_2H$ the value is 4.88. Benzoic acid, pK_a 4.17, comparable to acrylic acid.

One carboxyl group close to another increases the acidic strength, as seen from the pK_a values: HO_2CCO_2H (oxalic, 1.46); $HO_2CCH_2CO_2H$ (malonic, 2.80); $HO_2CCH_2CH_2CO_2H$ (succinic, 4.17). In the aromatic series: $HO_2CC_6H_4CO_2H$, *para*, 3.82; *meta*, 3.28; *ortho*, 3.00; $C_6H_5CO_2H$, 4.17.

Nitrophenols. A single NO_2 group *o*-, *m*-, or *p*- increases acidity of phenol from pK_a 10.0 to pK_a 7.2–8.0. 2,4-Dinitrophenol, 4.0; picric acid (trinitrophenol), 0.80.

Amines

Types: primary, RNH_2; secondary, R_2NH; tertiary, R_3N. Preparation by amination of a halogen compound. $RBr + NH_3$ ⟶ $RN^+H_3Br^-$; $RN^+H_3Br^- + NaOH$ ⟶ RNH_2. Formation of secondary amine suppressed by use of excess NH_3: $CH_3CHBrCO_2H$ + 70 equiv. of NH_3 ⟶ $CH_3CH(NH_2)CO_2H$ (alanine). Aniline + CH_3I ⟶ N-methylaniline and N,N-dimethylaniline. Quaternary ammonium salts: $(CH_3)_3N + CH_3Br$ ⟶ $(CH_3)_4N^+Br^-$. Primary amines by reduction of unsaturated N-compounds. $RC{\equiv}N$ (a nitrile) ⟶ RCH_2NH_2.

Basic strength measured by $pK_b = -\log k_b$. NaOH, pK_b about 0; a very weak base has value approaching the limit pK_b = 14. Ammonia, pK_b 4.7; CH_3NH_2, 3.4. $NH_4^+OH^-$ weak because of instability. Tetramethylammonium hydroxide is stable and is a strong base; prepared from $(CH_3)_4N^+I^-$ + AgOH.

Any unsaturated group linked to N decreases basic strength. Thus aniline is a weak base, pK_b 9.3. Aniline sufficiently basic to form stable salts with acids; salts are water-soluble ether-insoluble. Nitro groups, by induction, decrease basic strength of an arylamine.

Amides and Imides

Amides of the type $RCONH_2$ are obtained from an acid chloride + NH_3 and by partial hydrolysis of a nitrile. Amides of types CH_3CONHR and CH_3CONR_2 result from acetylation of a primary amine, H_2NR, or secondary amine, HNR_2, by reaction with acetic anhydride.

Amides of all above types are neutral (the acid-forming group balances base-forming nitrogen). Amides can be hydrolyzed, but are more stable to hydrolysis than esters. Thus the O,N-diacetate of *p*-aminophenol is hydrolyzed by cold alkali to the N-monoacetate.

Urea, H_2NCONH_2, is a product of metabolism of proteins excreted in the urine. Having two amino groups and only one acid-forming group, it is basic and forms a stable mononitrate, useful for isolation.

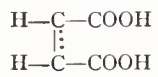
Succinimide and phthalimide have two carbonyl groups linked to N and activating the H; hence they are weak acids soluble in alkali.

Sulfonamides: $C_6H_5SO_2Cl$ + amine. Hinsberg test: primary amine ⟶ alkali-soluble derivative; secondary ⟶ alkali-insoluble derivative; tertiary, no reaction.

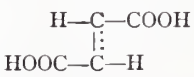
Lewis concept of an acid as an electron acceptor and a base as an electron donor. A proton (Lewis acid) combines with R_3N: (Lewis base, has a pair of unshared electrons). Trimethylboron is electron deficient and so functions as a Lewis acid: $(CH_3)_3B + :N(CH_3)_3 \longrightarrow (CH_3)_3B:N(CH_3)_3$. Neutralization is: H^+(acid) + OH^-(base) $\longrightarrow$ HOH. An ether acts as a Lewis base in formation of an oxonium salt: $(CH_3)_2O + H^+Cl^- \longrightarrow [(CH_3)_2O^+H]Cl^-$. Boron fluoride, an excellent catalyst for esterification and acylation, is an electron-deficient Lewis acid; gaseous BF_3 forms a liquid etherate: $(C_2H_5)_2O + BF_3 \longrightarrow (C_2H_5)_2O^+B^-F_3$.

PROBLEMS

1. Calculate the theoretical yield of methyl benzoate in the experiment photographed, with allowance for the benzoic acid recovered. What was the percentage yield?
2. Do you think that the same procedure of esterification and the same method of isolation of the product would be satisfactory as applied to *o*-hydroxybenzoic acid (salicylic acid)?
3. What products would you expect from the reaction of ketene with water and with ammonia?
4. Which geometrical isomer would you expect to be the more strongly acidic, maleic acid (*cis*) or fumaric acid (*trans*)?



Maleic acid



Fumaric acid

5. The acids listed below are all α-substituted acetic acids. From the pK_a values cited, arrange the substituent groups in the order of decreasing electron-attracting potency.

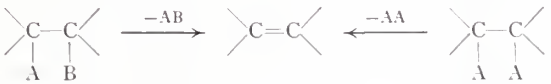
$HOCH_2CO_2H$	3.83	$ClCH_2CO_2H$	2.80
$CH_3OCH_2CO_2H$	3.48	$BrCH_2CO_2H$	2.87
$N{\equiv}CCH_2CO_2H$	2.44	ICH_2CO_2H	3.13
$HSCH_2CO_2H$	3.55	$C_6H_5CH_2CO_2H$	4.31

6. Do you suppose that the conventional formula for alanine, $CH_3CH(NH_2)COOH$, represents the true nature of the substance?
7. Each of the following compounds can be selectively hydrolyzed (reaction with just one mole of water). What are the products?
   (*a*) *p*-$CH_3OC_6H_4CO_2CH_3$
   (*b*) $CH_3CONHCH_2CO_2CH_3$
   (*c*) Phthalimide (9.24)

CHAPTER 10

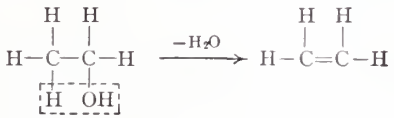
ELIMINATION REACTIONS

A typical elimination reaction is one involving simultaneous re- 10.1
moval of two atoms or groups from adjacent carbon atoms with production of a double bond. The entities eliminated are usually



different, for example, H and OH, or H and Br, but sometimes they are the same, as two atoms of bromine. The usual reaction products contain a double bond, but it is possible also to produce triple bonds and conjugated diene systems by elimination reactions.

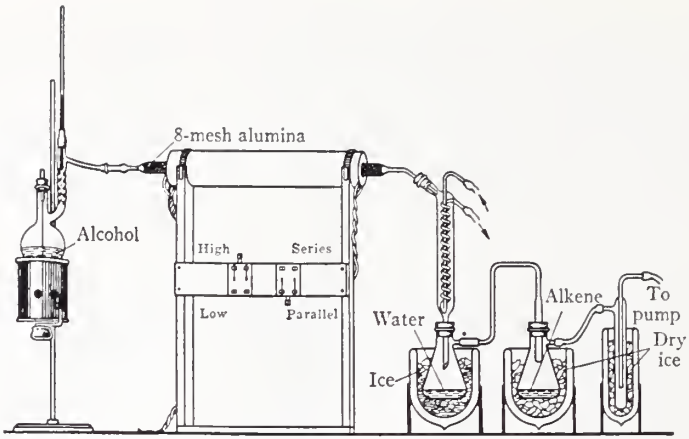
Dehydration. — Elimination of water from alcohols is a useful 10.2
method for the preparation of alkenes; thus on elimination of OH



from one carbon atom and of H from another, ethanol yields ethylene.

Several experimental procedures are available for effecting this 10.3
type of reaction. One procedure is catalytic dehydration. The alcohol is distilled through a tube packed with granules of alumina and maintained at a temperature of 350–400° in an electrically heated furnace. The reaction resembles pyrolysis of an alkane, since it involves production of an unsaturated product from a saturated one at an elevated temperature, but the pyrolysis temperature for an alcohol is distinctly lower, and the process is simpler and more uniform. A partial vacuum is sometimes advantageous in providing for removal of the alkene before secondary changes can occur, as in the apparatus shown on the following page.

Dehydration over alumina



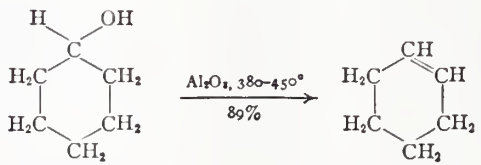
Apparatus for Dehydration of an Alcohol over Alumina at Reduced Pressure

Examples:

1. $CH_3CH_2OH \xrightarrow[98\%]{\text{Kaolin or alumina, } 350\text{–}360^\circ} CH_2{=}CH_2$

2. $CH_3{-}\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}CH_3 \xrightarrow[79\text{–}86\%]{Al_2O_3,\ 420\text{–}470^\circ} CH_2{=}\overset{\overset{CH_3}{|}}{C}{-}\overset{\overset{CH_3}{|}}{C}{=}CH_2$

Pinacol — 2,3-Dimethylbutadiene-1,3

3. 

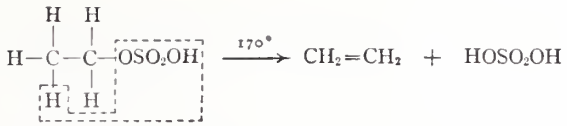
Cyclohexanol — Cyclohexene

10.4 *With sulfuric acid*

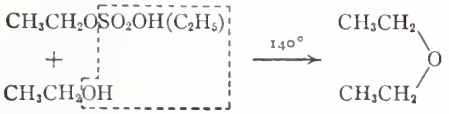
Another method of dehydration is with sulfuric acid in the temperature range 100–170°. When the acid is added to ethanol gradually with ice cooling, water is eliminated from the two reactants, and ethylsulfuric acid is formed. The reaction proceeds to completion

$$CH_3CH_2O\boxed{H + HO}SO_2OH \underset{\text{excess } H_2O}{\overset{\text{concd. } H_2SO_4}{\rightleftharpoons}} \underset{\text{Ethylsulfuric acid}}{CH_3CH_2OSO_2OH} + H_2O$$

with use of excess concentrated sulfuric acid at 0°, for the acid absorbs the water formed; the process, however, is an equilibrium, and the conversion can be reversed by use of a large excess of water. Ethylsulfuric acid was encountered earlier as the product of addition of sulfuric acid to ethylene (3.8); by pyrolytic decomposition it is convertible into ethylene, and hence the cycle is complete. At an optimum temperature of 170°, the chief organic product of decomposition is ethylene, formed by loss of the group OSO_2OH from one carbon atom



and of hydrogen from the adjacent position to produce sulfuric acid. A side reaction consists in formation of diethyl ether (ordinary ether) by the action of ethanol on ethylsulfuric acid. This reaction can be operated for the preparation of ether by adjusting the proportions of



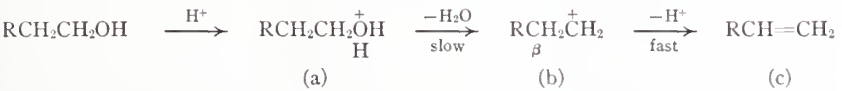
Ether a by-product

the reagents and maintaining a temperature of 140°. The difference in the optimum temperatures for ethylene and ether formation is so slight that each product is an inevitable by-product of the preparation of the other.

Dehydration can be effected also with hydrochloric acid, phosphoric acid, or potassium bisulfate ($KHSO_4$). These are strong acids, but they are incapable of forming intermediates analogous to an alkylsulfuric acid, and hence the following mechanism represents the more general case of acid-catalyzed dehydration. In the first step the alcohol functions as a Lewis base and accepts a proton to form an oxonium ion (a). This ion loses water to form a carbonium ion (b),

10.5

With HCl or $KHSO_4$



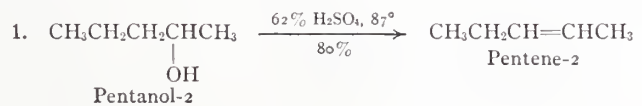
Mechanism

which expels hydrogen from the β-position together with the charge, as a proton, to produce the alkene (c). The terminal step is thus the same as in the formation of isooctene in the acid-catalyzed dimerization of isobutene (8.11). The reaction is unimolecular and the rate-determining step is loss of water from the (a) to form the carbonium ion (b); it is described as an E_1 reaction (unimolecular elimination).

Ease of Dehydration. — An invariable rule is that tertiary alcohols are dehydrated more readily than primary and secondary alcohols and that primary alcohols are the least readily dehydrated. These differences are illustrated in the accompanying examples. The secondary alcohol shown in example 1 is dehydrated in 80% yield at the temperature of the steam bath by 62% sulfuric acid, whereas the

10.6

Reactivity: tert > sec > prim



2. $CH_3CH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_3 \xrightarrow[84\%]{46\%\ H_2SO_4,\ 87^\circ} CH_3CH{=}\overset{\displaystyle CH_3}{C}CH_3$

2-Methylbutanol-2 — 2-Methylbutene-2

3. $\left(CH_3\right)_2\overset{\displaystyle OH}{C}CH_2CH_2\overset{\displaystyle OH}{C}HCH_3 \xrightarrow{\text{Catalyst}} \left(CH_3\right)_2C{=}CHCH_2CHCH_3$ (OH)

(Initial product)

4. Cyclohexanol $\xrightarrow[83\%]{95\%\ H_2SO_4,\ 130\text{–}140^\circ}$ Cyclohexene

tertiary alcohol of example 2 affords an alkene in comparable yield at the same temperature by acid of only 46% strength. The case of ethanol, cited above, is representative of the behavior of a primary alcohol; the best results are obtained with use of 96% (concentrated) sulfuric acid at the higher temperature of 170°. That a tertiary alcohol undergoes dehydration more easily than a secondary alcohol is further demonstrated by the behavior of the dihydroxy compound shown in example 3. This diol contains both a tertiary and a secondary alcoholic group, and on partial dehydration the former is preferentially eliminated. Example 4 shows that cyclohexanol can be dehydrated to cyclohexene by sulfuric acid as well as by the catalytic method cited above, although in slightly lower yield. This dehydration has been accomplished also with potassium bisulfate ($KHSO_4$), phosphoric acid, iodine, and oxalic acid, a dibasic acid of acidic strength nearly comparable to that of a mineral acid.

10.7 ***Explanation of differences in reactivity***

The reaction mechanism suggested above accounts adequately for the difference in reactivity of primary, secondary, and tertiary alcohols. A primary alcohol gives an intermediate carbonium ion stabilized

(*prim*) $RCH_2CH_2OH \xrightarrow{H^+} RCH_2\overset{+}{C}H_2OH \xrightarrow{-H_2O} RCH_2\overset{+}{C}H_2 \xrightarrow{-H^+} RCH{=}CH_2$

(*sec*) $RCH_2\underset{\displaystyle R}{\underset{|}{C}}HOH \xrightarrow{H^+} RCH_2\overset{+}{\underset{\displaystyle R}{\underset{|}{C}}}HOH \xrightarrow{-H_2O} RCH_2\overset{+}{\underset{\displaystyle R}{\underset{|}{C}}}H \xrightarrow{-H^+} RCH{=}\underset{\displaystyle R}{\underset{|}{C}}H$

(*tert*) $RCH_2\underset{\displaystyle R}{\underset{|}{C}}OH \xrightarrow{H^+} RCH_2\overset{+}{\underset{\displaystyle R}{\underset{|}{C}}}OH \xrightarrow{-H_2O} RCH_2\underset{\displaystyle R}{\underset{|}{C}}{}^+ \xrightarrow{-H^+} RCH{=}\underset{\displaystyle R}{\underset{|}{C}}R$

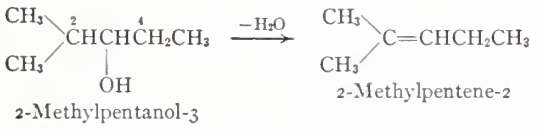
by only one electron-releasing alkyl group (RCH_2—), the intermediate from a secondary alcohol is stabilized by two such groups, and the carbonium ion from a tertiary alcohol has three electron-releasing groups. The order of reactivity thus follows the order of stability of the key intermediate carbonium ions.

10.8 **Direction of Dehydration.** — The structure of an alcohol may be

such that two routes of dehydration are open. In pentanol-2, hydrogen atoms adjacent to the hydroxylated carbon are available at both positions 1 and 3, but actually the latter hydrogen is utilized almost exclusively, and the chief product of dehydration is pentene-2. An alkene having a terminal double bond (pentene-1) is a less preferred

$$\underset{\text{Pentanol-2}}{CH_3CH_2\overset{3}{C}H_2\overset{2}{C}H(OH)\overset{1}{C}H_3} \xrightarrow{-H_2O} \underset{\text{Pentene-2}}{CH_3CH_2CH{=}CHCH_3}$$

product than an isomer with the ethylenic linkage in an interior position (pentene-2). In the case of 2-methylpentanol-3, removal of hydrogen from either of the alternate positions 2 or 4 would give an internal double bond, but nevertheless a definite preference exists,



2-Methylpentanol-3 2-Methylpentene-2

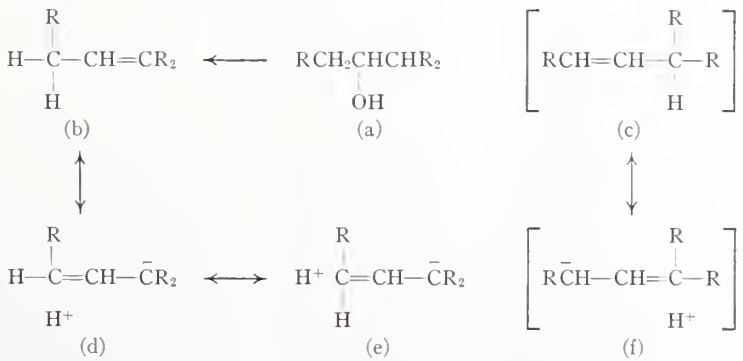
and the chief product is that resulting from abstraction of the hydrogen in the 2-position. The carbon atom at this position is tertiarily substituted and carries but one hydrogen, whereas at the alternate (secondary) position there are two. In the dehydration of pentanol-2 cited above, the hydrogen eliminated comes from a secondarily, rather than a primarily substituted carbon atom. These examples are representative and illustrate an empirical rule due to the Russian chemist Alexander M. Saytzeff (1875) that, in dehydration of alcohols, hydrogen is eliminated preferentially from the adjacent carbon atom that is poorer in hydrogen.*

Saytzeff rule (see Matthew)

A possible explanation of the facts summarized in the empirical rule is as follows. The alcohol (a) yields alkene (b) preferentially because charge separation in (b) gives the resonance structures (d) and

10.9

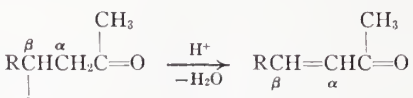
Theoretical interpretation



* Matthew XXV, 29, ". . . but from him that hath not shall be taken away even that which he hath."

(e). The postulated phenomenon is called no-bond resonance, or hyperconjugation. With the alternative alkene (c) only one no-bond resonance structure is possible (f) and resonance stabilization is not as great as in (b).

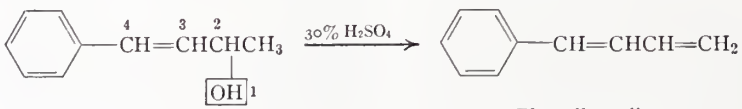
10.10 If an alcohol contains an appropriately located center of unsaturation, the unsaturated group may exert an activating influence sufficient to alter the course of dehydration. Thus the β-hydroxy ketone I has



I II

Driving force to form conjugated systems

α-hydrogen atoms activated by the carbonyl group and, regardless of the structure of the R group, loses water readily to form the α,β-unsaturated ketone II, a conjugated ketone stabilized by resonance. Another example is the unsaturated alcohol III, in which the hy-

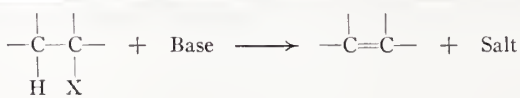


III IV

1-Phenylbutadiene-1,3

droxyl group is activated by the double bond and which loses water readily in the direction shown because the product (IV) has a resonance-stabilized conjugated diene system further stabilized by conjugation with the benzene ring.

10.11 **Dehydrohalogenation (Elimination of HX).** — Elimination of the elements of a hydrogen halide from an alkyl halide is another useful method of introducing a double bond. The reaction is accomplished by treating an alkyl halide with a basic reagent capable of splitting out the elements of hydrogen halide from adjacent carbon atoms:

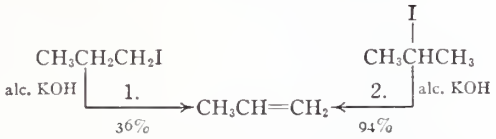


Alcoholic KOH

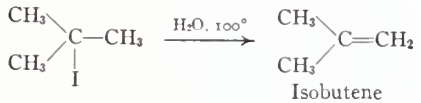
An acid-binding reagent commonly employed is an alcoholic solution of potassium hydroxide. Aqueous alkali is less suitable because of lack of solubility of the alkyl halide in water; alcohol is a satisfactory solvent for the organic reagent and also dissolves potassium hydroxide. The elimination is an E_2 reaction, that is, a bimolecular elimination, but nevertheless the rules describing the relative ease and the direction of dehydration of alcohols apply also to the dehydrohalogenation of alkyl halides. Thus tertiary halides are the most reactive and primary halides the least reactive, and hydrogen is eliminated preferen-

Rules for dehydration applicable

tially from the carbon atom poorest in hydrogen. Propylene can be obtained from either *n*-propyl iodide (1) or isopropyl iodide (2), but the yield is notably better with the secondary than with the primary iodide (temperature in each case, 80–100°). The tertiary iodide shown

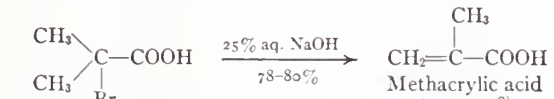


in example 3 reacts so readily that the alkene is obtained simply by addition of the halide dropwise to boiling water, which retains the hydrogen iodide formed. The method finds little use in the prepara-



Isobutene

tion of ethylenic hydrocarbons themselves, for the required alkyl halides are best obtained from the corresponding alcohols and a shorter route from the alcohol to the alkene is direct dehydration. The occasion for introduction of a double bond, however, arises in other series; for example, a double bond can be introduced into isobutyric acid by bromination, followed by elimination of hydrogen



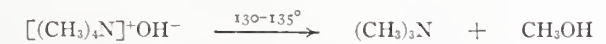
α-Bromoisobutyric acid
Methacrylic acid
(m.p. 15°)

bromide. Vinyl chloride, a key chemical for the manufacture of plastics, is produced as a petrochemical from ethylene by thermal dehydrohalogenation of ethylene dichloride.



Vinyl chloride

Hofmann Degradation. — In 1851 A. W. von Hofmann discovered 10.12
an interesting reaction of quaternary ammonium hydroxides, $R_4N^+OH^-$. These substances, in contrast to ammonium hydroxide, are stable at room temperature, but when heated to moderate temperatures they decompose smoothly to two products. Tetramethylammonium hydroxide when heated to 130° decomposes to trimethylamine and methanol. Other quaternary bases likewise undergo thermal de-



Tetramethylammonium hydroxide

Elimination of methanol

composition, but if the alkyl group eliminated in the process contains two or more carbon atoms the nitrogen-free reaction product is not the alcohol but the corresponding alkene. Thus tetraethylammonium hydroxide when heated breaks down into triethylamine, ethylene,

$$[(CH_3CH_2)_4N]^+OH^- \xrightarrow{100^\circ} (CH_3CH_2)_3N + CH_2{=}CH_2 + H_2O$$

(tetrahydrate, m.p. 50°)

Alkene formation

and water. This behavior is typical of the bases as a class, and formation of an alcohol in the one instance where production of an alkene is impossible represents a special case. Furthermore, elimination of a methyl group as methanol occurs less readily than the splitting off of any higher alkyl group as the alkene. If the hydroxide contains both methyl and ethyl groups, as in $[(CH_3)_3NCH_2CH_3]^+OH^-$ or $[(CH_3CH_2)_3NCH_3]^+OH^-$, decomposition invariably affords ethylene and not methanol. When a still higher group competes with methyl, the latter holds fast to nitrogen and the higher group is severed with loss of a β-hydrogen and formation of an alkene. The decomposition proceeds readily and in good yield at moderate tem-

$$(CH_3)_3\overset{+}{N}\text{—}\overset{|}{\underset{|}{C}}\text{—}\overset{|}{\underset{\beta}{CH}}\text{—} \longrightarrow (CH_3)_3N + \overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}} + H_2O$$

OH^-

peratures; it often can be effected by merely boiling an aqueous solution of the base.

10.13 Hofmann saw in this smoothly occurring reaction and in the greater firmness of attachment of methyl than of other groups a general scheme applicable both to determination of structures of amines and to preparation of ethylenic compounds. The first step consists in treating an amine with excess methyl iodide to replace all available amino hydrogens by methyl groups and then to produce the quaternary salt or methiodide from the tertiary amine (exhaustive methylation). Analysis reveals whether the starting material is a primary, secondary, or tertiary amine, for these types allow the introduction of three, two, or one methyl group, respectively. The iodide is then converted with moist silver oxide into the quaternary ammonium hydroxide and this is pyrolyzed. In special cases such a

Exhaustive methylation and decomposition of $R_3N^+OH^-$

$$RCH_2CH_2NH_2 \xrightarrow{CH_3I} RCH_2CH_2\overset{+}{N}(CH_3)_3\,I^- \xrightarrow{AgOH} RCH_2CH_2\overset{+}{N}(CH_3)_3\,OH^- \xrightarrow{Heat} RCH{=}CH_2$$

process is preferred for preparation of alkenes. If an amine of unknown structure is under investigation, it can be degraded by the Hofmann procedure into a simpler, nitrogen-free substance having an unsaturated center of assistance in further characterization. Many

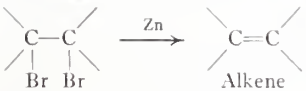
Structure determination

naturally occurring nitrogen bases of elaborate structure have been profitably investigated by this method.



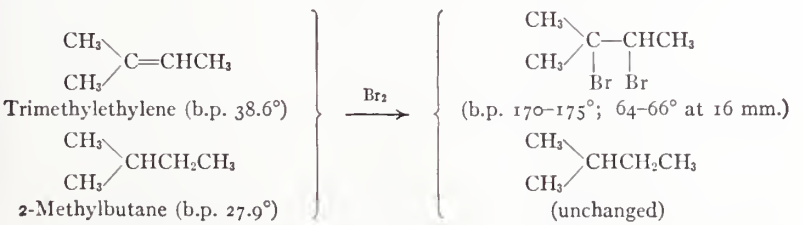
August Wilhelm von Hofmann, 1818–92
Born at Giessen, Germany; Professor at Bonn, Germany; then at the Royal College of Chemistry, London (1845–64); then at Berlin; one-time president of both the Chemical Society (London) and the German Chemical Society.

***vic*-Dibromides.** — The addition of bromine to an alkene to form a *vic*-dibromide can be reversed by the action of bivalent zinc, which eliminates the two halogen atoms simultaneously. The chief use of 10.14



vic-Dibromide Alkene

this elimination reaction is in the purification of ethylenic compounds. An alkene can be converted into its bromine-addition product and subsequently regenerated by reduction with zinc dust, with advantages that can be appreciated from an example. A sample of trimethylethylene contaminated with the corresponding saturated hydrocarbon, 2-methylbutane (isopentane), could not be separated from this substance by ordinary distillation because the boiling points lie too close together. If the mixture is treated with bromine without undue



Purification of an alkene

exposure to light, the alkene reacts selectively and is converted into a derivative heavier by some 160 units of molecular weight and consequently having a very much higher boiling point. Trimethylethylene dibromide boils at a temperature 140–145° higher than 2-methylbutane, and can be separated easily and completely by vacuum distillation. By treatment of the distilled addition product with zinc dust in alcoholic solution, pure trimethylethylene is regenerated. An ethylenic compound that is a solid can be purified by conversion to its *vic*-dibromide, which is invariably less soluble than the parent substance and than nonethylenic companion substances and therefore easily purified by crystallization. The pure derivative is then debrominated with zinc dust.

10.15 Alkynes

vic-Dibromides are convertible into acetylenes by another elimination reaction, namely by elimination of two molecules of hydrogen halide by treatment with alcoholic potassium hydroxide. Thus one method for introduction of the triple bond is the sequence of reactions:

$$-CH{=}CH- \xrightarrow{Br_2} -\underset{Br}{CH}-\underset{Br}{CH}- \xrightarrow{\text{alc. KOH}} -C{\equiv}C-$$

When bromine is added to the double bond of propylene and the product is treated with potassium hydroxide in alcohol, the unsaturated hydrocarbon produced is essentially pure methylacetylene. A possible

C—C≡C more stable than C=C=C

$$CH_3CH(Br)-CH_2(Br) \xrightarrow{\text{alc. KOH}} \begin{cases} \xrightarrow{\text{Chief product}} CH_3C{\equiv}CH \text{ (more stable)} \\ \text{Methylacetylene} \\ \xrightarrow{\text{Trace only}} CH_2{=}C{=}CH_2 \text{ (less stable)} \\ \text{Allene} \end{cases}$$

alternative course of the reaction would involve elimination of hydrogen bromide between the 2-bromo atom and a hydrogen of the adjacent methyl group to give allene, $CH_2{=}C{=}CH_2$. This diene, however, appears in no more than traces; allenes are labile and show a marked tendency to rearrange to the more stable acetylenic isomers. A *vic*-dihalide of the type $RCH_2CHBrCHBrCH_2R$ on dehydrohalogenation may afford either the acetylene or the conjugated diene, $RCH{=}CHCH{=}CHR$, or a mixture of both. The dibromide of the methyl ester of oleic acid when refluxed with potassium hydroxide in *n*-butyl alcohol affords an evident mixture from which, however, the acetylenic product stearolic acid is isolated easily if in low yield. In an improved procedure the dehydrobromination is done with sodamide

$$\underset{\text{Methyl oleate}}{CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3} \xrightarrow[\text{2. KOH}]{\text{1. } Br_2} \xrightarrow[40^{\circ}C]{} \underset{\text{Stearolic acid}}{CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH}$$

($NaNH_2$) in liquid ammonia and the yield of stearolic acid is raised to 68%.

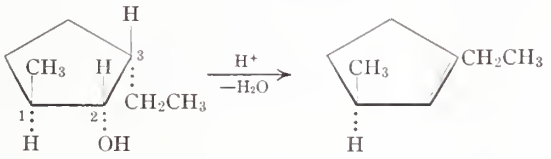
Steric Course of Eliminations. — The elimination of bromine from a *vic*-dibromide is the counterpart of the reaction in which the dibromide is formed. It has been noted that bromination takes the course of *trans*-addition, with the two bromines approaching from opposite sides. In the reverse reaction, *trans*-elimination seems to be the normal, preferred route. Thus debromination of *trans*-cyclopentene dibromide (1) is considerably faster than debromination of



(1) *trans* (2) *cis*

trans-Elimination the normal course

the *cis*-isomer (2). The same preference for *trans*-elimination holds for all ionic eliminations, that is, for dehydrohalogenation with base and for acid-catalyzed dehydration of alcohols. This steric factor sometimes determines the direction in which elimination occurs. Thus the methylethylcyclopentanol (3) is capable of undergoing dehydra-



(3) (4)

trans-Dehydration preferred to cis

tion in either of two directions. Each carbon adjacent to the hydroxylated carbon carries one hydrogen, and hence there is no preference in the direction of elimination from the point of view of the Saytzeff rule. However, utilization of the hydrogen at C_1 would require *cis*-elimination, whereas utilization of the hydrogen at C_3 would involve the more normal *trans*-elimination. Hence the compound would be expected to undergo *trans*-elimination and give (4), in which the ethyl rather than the methyl group is attached to the double bond. *trans*-Elimination has been so well established in more complicated cases that there is little doubt that this prediction could be verified.

SUMMARY

Dehydration (elimination of HOH). (*a*) Catalytic dehydration over alumina at 450°. $CH_3CH_2OH \longrightarrow CH_2{=}CH_2$. Pinacol $\longrightarrow$ 2,3-dimethylbutadiene-1,3. Cyclohexanol $\longrightarrow$ cyclohexene. (*b*) With H_2SO_4 at 100–170°. Initial product an ester of sulfuric acid:

$$CH_3CH_2OH \longrightarrow CH_3CH_2OSO_2OH \longrightarrow (\text{heat})\ CH_2{=}CH_2 + HOSO_2OH.$$

Ether formed as by-product. (*c*) Acid-catalyzed dehydration (HCl, H_3PO_4, $KHSO_4$). Mechanism:

$$RCH_2CH_2OH \xrightarrow{H^+} RCH_2CH_2O^+H_2 \longrightarrow RCH_2C^+H_2 \xrightarrow{-H^+} RCH{=}CH_2.$$

An E_1 reaction (elimination of 1st order = unimolecular).

Order of reactivity of alcohols: tertiary > secondary > primary. Explanation: the intermediate carbonium ion is stabilized by electron-release by three alkyl groups in a tertiary alcohol, by two in a secondary, and by only one in a primary alcohol.

Direction of dehydration. Saytzeff rule: hydrogen is eliminated preferentially from the adjacent carbon poorer in hydrogen. Explanation: the alkene formed is the one of maximum stabilization by no-bond resonance (hyperconjugation).

Activation of OH by an unsaturated group. A β-hydroxy ketone loses water readily because the product is a resonance-stabilized conjugated ketone:

$$RCH(OH)CH_2C(=O)CH_3 \longrightarrow RCH{=}CHC(=O)CH_3.$$

$$C_6H_5CH{=}CHCH(OH)CH_3 \longrightarrow CH_3CH{=}CHCH{=}CH_2.$$

Dehydrohalogenation (elimination of HX). Rules for dehydration applicable: tertiary > secondary > primary; preferential elimination of H from H-poor carbon. Introduction of double bond:

$$(CH_3)_2CHCO_2H \longrightarrow (CH_3)_2CBrCO_2H \longrightarrow CH_2{=}C(CH_3)CO_2H$$

Vinyl chloride by thermal dehydrohalogenation of $ClCH_2CH_2Cl$.

Hofmann degradation: formation of an alkene by pyrolysis of a quaternary ammonium hydroxide,

$$RCH_2CH_2N^+(CH_3)_3OH^- \longrightarrow RCH{=}CH_2 + N(CH_3)_3 + H_2O.$$

Methyl always remains fixed to N and a higher group is eliminated as an alkene. Useful in structural determination. An amine is exhaustively methylated, converted through the quaternary ammonium iodide to the quaternary ammonium hydroxide, and this is pyrolyzed.

Debromination of a *vic*-dibromide: $R_2CBrCBrR_2$ + Zn dust in acetic acid $\longrightarrow R_2C{=}CR_2$. Purification of a crude alkene by conversion to a higher-boiling liquid or a less soluble dibromide and regeneration from the purified derivative.

Dehydrohalogenation of a *vic*-dibromide to an acetylene (more stable than the isomeric allene, $CH_2{=}C{=}CH_2$).

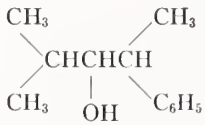
Steric course of elimination: *trans*-elimination the normal path for ionic dehydration, dehydrohalogenation, or debromination. Thus *trans*-cyclopentene dibromide is debrominated faster than *cis*-isomer.

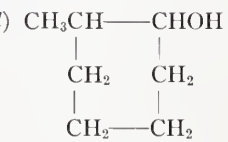
PROBLEMS

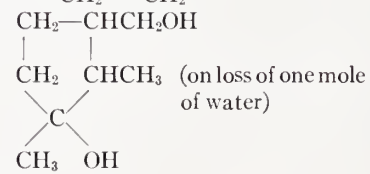
1. What products would you expect to result from acid-catalyzed dehydration of each of the following alcohols?

(*a*) $C_6H_5CH_2CH_2CHCH(CH_3)_2$ (OH)

(*b*) $CH_3CH_2CHCH{=}CHCH_3$ (OH)

(*c*) 

(*d*) 

(*e*) 

2. Predict the products of the reaction of each of the following with alcoholic potassium hydroxide.

(*a*) $C_6H_5CH_2CHCH_2CH_3$ (with Br on the CH)

(*b*) $CH_3CH_2CHCHCH_2CH_3$ (with Br on each CH)

(*c*) $C_6H_5CH_2CHCHCH_2C_6H_5$ (with Br on each CH)

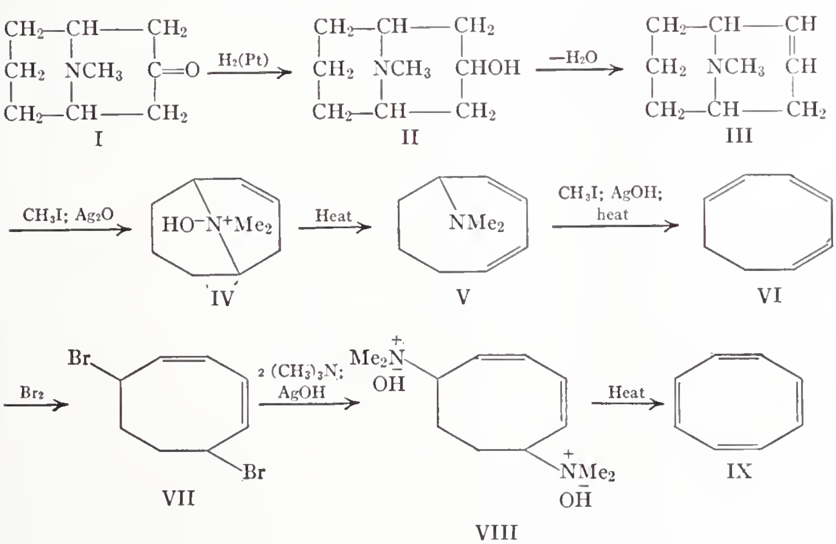
(*d*) $CHBr_2CHBr_2$

3. Glycerol, $HOCH_2CHOHCH_2OH$, on treatment with sulfuric acid loses two moles of water and gives a product of the formula C_3H_4O. Deduce the structure of the product (decide how the first molecule of water is eliminated, and then deduce the ensuing steps).
4. How could phenylacetylene be obtained from styrene (6.22)?
5. The French chemist C. Tanret in 1878 isolated from pomegranate root four alkaloids (basic = alkali-like) and named them in honor of a compatriot, P. J. Pelletier. One, pseudopelletierin, was investigated by G. Ciamacian in Italy and by R. Willstätter in Germany and shown to have the bicyclic structure I. In 1913 Willstätter employed the alkaloid as starting material for the synthesis of cyclooctatetraene (IX) in order to determine if this hydrocarbon, with a closed, cyclic, conjugated system, would have aromaticity comparable to that of benzene. Willstätter found this not to be the case; cyclooctatetraene is highly reactive and unstable and wholly unlike benzene. The full significance of the observation was not at the time apparent because the stability of benzene was not yet recognized as due to resonance. Whereas the benzene ring is planar, the cyclooctatetraene ring is puckered, with four carbons above the central plane and four below it. Cyclooctatetraene is incapable of stabilization through resonance, because migration of double and single bonds to new positions would involve movement of carbon atoms, and such a movement would violate a requirement for resonance.

   The problem is to account for the steps in the synthesis as formulated (Me = methyl).
6. How could you distinguish experimentally between the following isomers?

$$HOCH_2CH(CH_3)CH_2CH_2CH(CH_3)CH_2OH$$

$$HOCH_2CH_2CH(CH_3){-}CH(CH_3)CH_2CH_2OH$$



CHAPTER 11

REPLACEMENT REACTIONS

ALKYL HALIDES AND ALCOHOLS

11.1 The terms replacement and substitution are alternative descriptions of a reaction in which one atom or group takes the place of another, as in the formation of an alkyl halide from an alcohol, $ROH + HBr \longrightarrow RBr + H_2O$, or the reverse process of hydrolysis, $RI + AgOH \longrightarrow ROH + AgI$. Since the word substitution is usually used to describe introduction of a group in place of hydrogen in the benzene ring, and since most of the reactions discussed in this chapter involve groups other than hydrogen, these reactions are described here as replacements.

11.2 **Reactions of Alkyl Halides.** — One replacement is the reaction of an alkyl halide with the sodio derivative of an alcohol, or sodium

Williamson synthesis

$$\begin{matrix} CH_3I + NaOCH_2CH_2CH_3 \\ CH_3ONa + BrCH_2CH_2CH_3 \end{matrix} \searrow\!\!\nearrow \; CH_3OCH_2CH_2CH_3$$

Methyl-*n*-propyl ether

alkoxide, to form an ether. The reaction is named after the discoverer, the Englishman Alexander W. Williamson. A mixed ether can be prepared in two ways, as shown in the example formulated. Another replacement is that of an alkyl iodide with silver hydroxide formulated above; this is useful for the preparation of alcohols.

11.3 Another reaction which, though of somewhat different type, can be regarded as a replacement is that of an alkyl halide with metallic magnesium to form an alkylmagnesium halide. Thus methyl iodide reacts with magnesium suspended in ether (diethyl ether) to give ether-soluble methylmagnesium iodide. The magnesium, employed

Grignard reagent

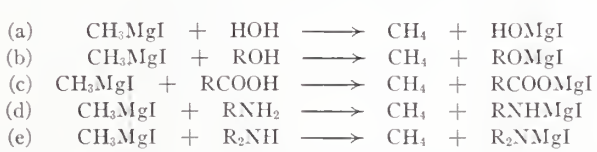
$$CH_3I + Mg \xrightarrow{\text{Ether}} CH_3MgI$$

Methylmagnesium iodide

as thin turnings or granules of the metal, gradually dissolves as the reaction proceeds. Ether is not merely a convenient solvent but forms a complex, a dietherate of the formula $CH_3MgI \cdot 2(C_2H_5O)$. The reaction proceeds satisfactorily with chlorides, bromides, and iodides, whether primary, secondary, or tertiary. The alkylmagnesium halides were discovered by the French chemist Victor Grignard in 1901 and they proved so extraordinarily useful in syntheses of types to be described in the next chapter that Grignard was awarded the Nobel Prize for 1912. The reagents, which enter into a variety of Grignard syntheses, are known as Grignard reagents.

11.4

Methylmagnesium iodide undergoes a replacement reaction which is rapid, quantitative, and of analytical value, namely reaction with water (a) with liberation of methane. Any compound which, like



(a) $CH_3MgI + HOH \longrightarrow CH_4 + HOMgI$
(b) $CH_3MgI + ROH \longrightarrow CH_4 + ROMgI$
(c) $CH_3MgI + RCOOH \longrightarrow CH_4 + RCOOMgI$
(d) $CH_3MgI + RNH_2 \longrightarrow CH_4 + RNHMgI$
(e) $CH_3MgI + R_2NH \longrightarrow CH_4 + R_2NMgI$

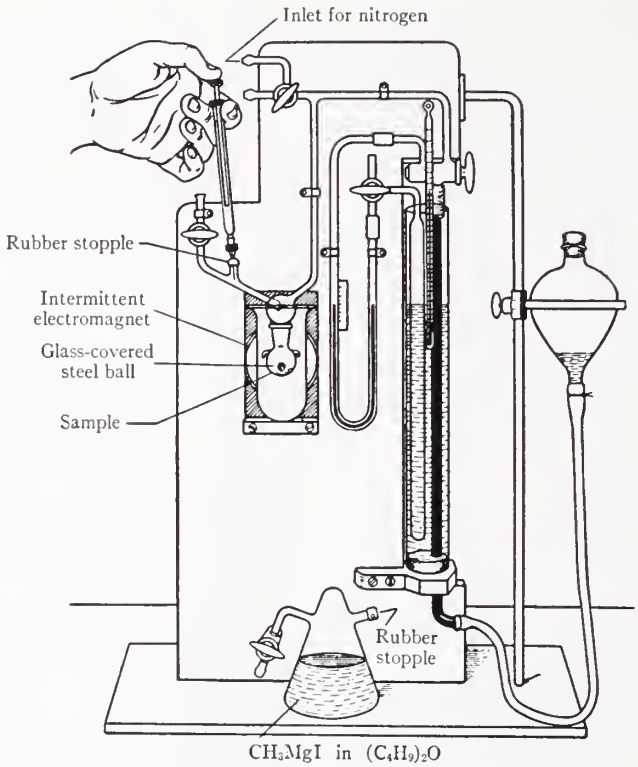
Active hydrogen

water, is capable of liberating methane from the methyl Grignard reagent is said to have active hydrogen. Alcohols of all types (b), acids (c), primary amines (d), and secondary amines (e) all have an active hydrogen atom. Only one of the two hydrogens of water reacts; a primary amine similarly has only one active hydrogen. The reaction is the basis of the Zerewitinoff method for the determination of the number of active hydrogens present in a given compound. The drawing on page 174 shows an apparatus for micro Zerewitinoff determination. A weighed sample is placed in the small round flask, which is then attached by a ground glass joint. The apparatus is flushed out with dry nitrogen, and then, by suitable manipulation of stopcocks and adjustment of the mercury leveling bulb, the burette is filled with mercury, with the inside pressure equal to the atmospheric pressure. A measured volume of Grignard solution (excess) is withdrawn from a reservoir with a hypodermic syringe and introduced in the manner shown, which prevents exposure to moist air. The mixture of sample and solution is stirred by the oscillation of the glass-covered steel ball and the methane evolved passes into the burette. After adjustment of pressure, the volume of gas is recorded. From the value found, and from the weight of sample and molecular weight of the substance, it is possible to calculate the number of active hydrogens present.

Zerewitinoff determination

11.5

Hydrolysis of Alkyl Halides. — A kinetic study consists in measurement of reaction rate and determination of the effect on reaction rate of variations in the conditions of the reaction and in the concen-



Apparatus for microdetermination of active hydrogen atoms

Useful in kinetic studies (reaction rates)

trations of reactants. A reaction of no preparative value but one which, nevertheless, has proved useful for the acquisition of accurate kinetic data, is alkaline hydrolysis of alkyl halides in very dilute solution in alcohol-water mixtures. In the hydrolytic replacement as applied to normal, saturated chlorides, bromides, and iodides, the methyl homolog is distinctly more reactive (from 5 to 20 times) than the ethyl and higher homologs, and the reactivity remains essentially constant from the ethyl homolog on:

Order of alkyl reactivity

$$CH_3X > CH_3CH_2X, \quad CH_3CH_2CH_2X, \quad CH_3CH_2CH_2CH_2X, \text{ etc.}$$

A second generalization is that a given iodide is more reactive than the corresponding bromide, which in turn surpasses the chloride, and this the fluoride:

Order of halide reactivity

$$RI > RBr > RCl > RF$$
$$C_6H_5I > C_6H_5Br > C_6H_5Cl > C_6H_5F$$

The differences here are even more pronounced than between a methyl and an ethyl halide and are observable, for example, in the speed of reaction with magnesium in the presence of ether.

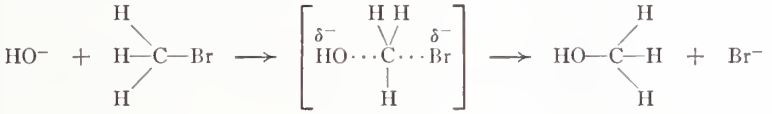
11.6 Mechanism of Hydrolysis. — Study of the rates of hydrolysis of primary, secondary, and tertiary alkyl halides disclosed an at first

perplexing relationship. In the series of alkyl bromides, for example, secondary bromides are hydrolyzed much more slowly than primary bromides, but tertiary bromides, instead of being hydrolyzed at a still slower rate, are hydrolyzed even faster than primary bromides. Kinetic studies by the Ingold school eventually explained the apparent anomaly. In the hydrolysis of methyl, ethyl, and isopropyl bromide

Hydrolysis is bimolecular

$$[HO^- + R]\!:Br \longrightarrow HOR + Br^-$$

the reaction rate is increased by an increase in concentration of either OH^- or RBr and hence the key step must involve collisions between molecules of alkyl halide and nucleophilic hydroxide ions. The reaction rate depends upon the concentration of two reactants and therefore the reaction is described as bimolecular. The hydrolysis is thus an S_N2 reaction (nucleophilic substitution = replacement; two reactants). A generally accepted mechanism advanced by Ingold postulates that the two reactants combine to form an intermediate complex or transition state. The bromine atom of methyl bromide is electronegative and repels the negative hydroxide ion, and the latter attacks the opposite side of the carbon, or the back side. In the transition state the hydroxyl group is partially attached to carbon, the bond to bromine is weakened (dotted lines), and the original charge of the hydroxide ion is distributed evenly between the entering and departing groups; the three hydrogen atoms and the carbon of the methyl group are in a plane at right angles to the line connecting OH



Transition state

Mechanism of S_N2 reaction of primary and secondary halides

and Br. Attack by hydroxide ion and expulsion of bromide ion from the complex are synchronous processes.

Reactivity to hydrolytic agents drops markedly in the series 11.7 methyl, ethyl, and isopropyl bromide, as shown by the following relative reaction rates (80% ethanol at 55°): CH_3Br, 100; CH_3CH_2Br, 8.0; $(CH_3)_2CHBr$, 0.2. This progressive decrease in reactivity is attributable to an inductive effect, an electron displacement that can be represented by an arrow pointing in the direction of the drift of electrons (B→A). In ethyl bromide the electron-releasing methyl joined to the carbon undergoing substitution inhibits attack by hydroxide ion, and in isopropyl bromide the inductive effect of two methyl groups results in still greater impediment to approach of the nucleophilic agent. In tertiary butyl bromide the combined inductive

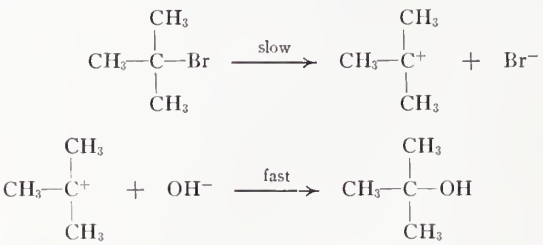
effect of three methyl groups completely suppresses the bimolecular reaction and hydrolysis proceeds unimolecularly; that is, the reaction

Inductive effects

$$CH_3{\rightarrow}CH_2Br \qquad \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CHBr$$

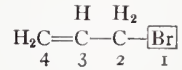
rate is dependent only on the concentration of alkyl bromide and is not increased by an increase in concentration of hydroxide ion. In the unimolecular reaction the rate-determining step is ionization of the halide to form a carbonium ion, which then combines with hydroxide ion as rapidly as it is formed. Ionization is promoted by stabilization of the ion by the combined electron release of the three alkyl groups.

Mechanism of S_N1 reaction of t-halides



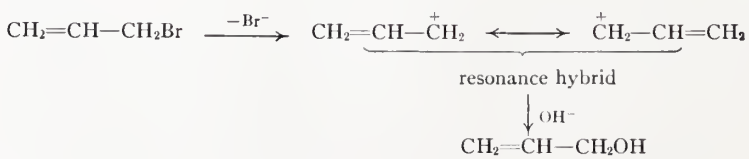
11.8 Allyl-Type Halides. — In a typical replacement reaction allyl chloride, $CH_2{=}CHCH_2Cl$, reacts many times as fast as the corresponding saturated chloride, $CH_3CH_2CH_2Cl$. Allyl bromide and iodide show corresponding enhanced reactivity. If the double bond is at a site more distant from the halogen atom, as in $CH_2{=}CHCH_2CH_2X$ or $CH_2{=}CHCH_2CH_2CH_2X$, no enhancement in reactivity over that of the corresponding saturated halides is observed. The phenomenon is a further example of the activation of an atom in position 1 by a 3,4-double bond:

Enhanced reactivity



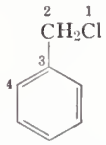
An explanation of the enhanced reactivity of allyl compounds is afforded by the resonance theory. Kinetic studies have shown that the hydrolysis of allyl bromide is unimolecular and hence indicate that the rate-controlling step is ionization to a carbonium ion. The allyl ion is a resonance hybrid, and resonance stabilizes this ion and

Explanation of reactivity



promotes its formation, and hence promotes hydrolysis. The double bond in the allyl position has an activating effect because it affords opportunity for resonance.

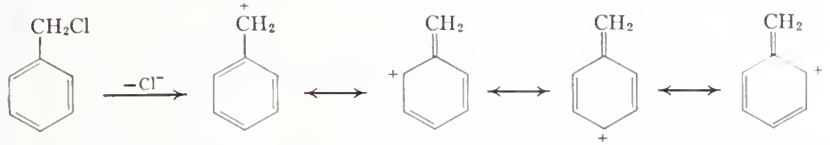
Benzyl chloride also shows greatly enhanced reactivity as compared with ordinary alkyl chlorides, and benzyl halides are appropri- 11.9



Benzyl chloride

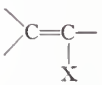
High reactivity

ately described as of the allyl type. Activation in benzyl chloride is likewise attributed to a tendency to form an intermediate carbonium ion stabilized by resonance. Here resonance establishes positive centers at the *ortho* and *para* positions in the nucleus, as well as in the side chain, as shown in the formulas.



Vinyl-Type Halides. — In contrast with allyl bromide, vinyl bro- 11.10 mide is peculiarly unreactive. A halogen atom directly attached to an ethylenic carbon atom displays definitely diminished reactivity as

$CH_2{=}CHBr$
Vinyl bromide

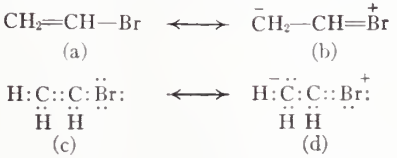


Vinyl halide type

Diminished reactivity

compared with the halogen of the corresponding saturated alkyl halide. Even vinyl iodide, under the usual conditions, does not react satisfactorily with magnesium to produce a Grignard reagent.

The inert character of the bromine atom in vinyl bromide (a) is 11.11 interpreted as due to resonance involving the polarized structure (b).

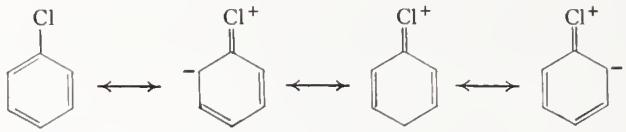


An effect of resonance

The corresponding electronic formulations are (c) and (d). In consequence of the resonance effect, bromine is held to carbon by a linkage that has a certain double-bond character and that is therefore shorter (1.86 Å) than the normal C—Br bond (1.91 Å) and less labile.

11.12 The diminished reactivity of halides of the vinyl type finds a parallel in the character of halides of the aromatic series, or aryl halides (ArX). Resonance involving the benzene ring shortens the

Aryl halides



carbon–chlorine bond and reduces reactivity to the extent that chlorobenzene does not form a Grignard reagent. Fortunately bromobenzene, although considerably less reactive than alkyl bromides, is reactive enough to form a Grignard reagent, phenylmagnesium bromide:

$$C_6H_5Br + Mg \xrightarrow{\text{Ether}} C_6H_5MgBr$$

11.13 **Conversion of Alcohols to Alkyl Halides.** — Whereas the alkaline hydrolysis of alkyl halides in very dilute solution just discussed is of theoretical rather than practical interest, the reverse reaction is very useful for the production of alkyl halides required as starting materials in various syntheses. A procedure applicable to the preparation of alkyl bromides and iodides of nearly all types consists in heating the alcohol with constant-boiling hydrobromic acid (47.5%) or hydriodic acid (57%). Hydrochloric acid is less reactive than hydrobromic or hydriodic acid and the constant-boiling material contains only 20%

Bromides and iodides

$$ROH + \underset{\text{(HBr or HI)}}{HX} \longrightarrow RX + H_2O$$

of HCl and the concentrated acid contains only 37% HCl; hence the HX-reaction ordinarily is not applicable to the preparation of alkyl chlorides. These substances can be prepared, however, by reaction of the alcohol with phosphorus trichloride:

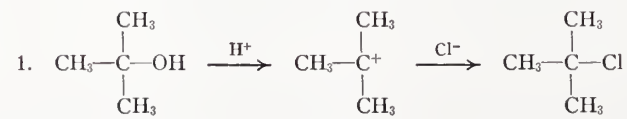
Chlorides

$$3\,ROH + PCl_3 \longrightarrow 3\,RCl + P(OH)_3$$

11.14 There are two exceptions to the rule that alcohols are ordinarily not convertible into the corresponding chlorides by reaction with hydrochloric acid. Both *t*-butyl alcohol and allyl alcohol are convertible into chlorides by the action of aqueous hydrochloric acid at moderate temperatures. Both reactions proceed by the S_N1 mecha-

Special cases

t-Alcohols



nism. *t*-Butyl chloride can be prepared by merely shaking the alcohol with concentrated hydrochloric acid for a few minutes in a separatory funnel at room temperature. The three alkyl groups promote forma-

tion of a stabilized carbonium ion intermediate (1). In allyl alcohol the hydroxyl group is in a position to be activated by the 3,4-double

Allyl alcohol

$$\overset{4}{H_2C}=\overset{3}{C}(H)-\overset{2}{C}(H_2)-\overset{1}{\boxed{OH}}$$

bond, and it readily separates to give a resonance-stabilized ionic intermediate (2).

2. $CH_2{=}CHCH_2OH \xrightarrow{-OH^-} CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH_2 \xrightarrow{Cl^-} CH_2{=}CHCH_2Cl$

ALLYLIC SUBSTITUTION

Glycerol from Petroleum. — Glycerol, which is propane-1,2,3-triol, is produced as a by-product in the manufacture of soap from fats in amounts sufficient except in time of war, when large amounts are required for conversion into the trinitrate ester, known by the com- 11.15

$$\begin{array}{l}CH_2OH\\|\\CHOH\\|\\CH_2OH\\\text{Glycerol}\end{array} + 3\,HONO_2 \xrightarrow[94\%]{H_2SO_4} \begin{array}{l}CH_2ONO_2\\|\\CHONO_2\\|\\CH_2ONO_2\\\text{Nitroglycerin}\end{array}$$

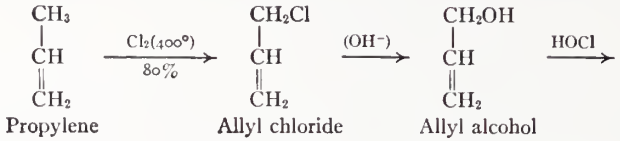
mon name nitroglycerin. Nitroglycerin, a liquid, is a powerful explosive but is too sensitive to shock to be used as such. Alfred Nobel in Sweden discovered (1866) that nitroglycerin can be absorbed in diatomaceous (porous) earth and compounded into the safe, practical explosive dynamite. Later (1875) Nobel discovered that guncotton, a cotton-like material which is an ester, cellulose trinitrate, $[C_6H_7O_2(ONO_2)_3]_n$, can be gelatinized with nitroglycerin to give a jelly of satisfactory stability and powerful explosive properties. The mutual solubility of the two trinitrate esters, one a solid and the other a liquid, is an example of the principle that like dissolves like. Smokeless powder suitable for use as a propellant in shells is now made from nitroglycerin (30%), guncotton (65%), and Vaseline (5%); the mixture is plasticized with acetone, extruded as rods, and dried to evaporate the acetone.

Glycerol and nitroglycerin

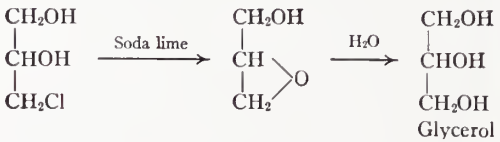
Dynamite and smokeless powder

In 1938 the Shell Oil Company in California announced production from petroleum of glycerol, an addition to the list of petrochemicals. The Shell process utilizes propylene produced by cracking and involves high-temperature chlorination to allyl chloride and the series of subsequent steps formulated. The reactions of hydrolysis to allyl alcohol, addition of hypochlorous acid (in accordance with the Markownikoff rule), and formation of an ethylene oxide follow the pattern of reactions described earlier; the terminal step involves opening of an 11.16

ethylene oxide ring by reaction with water to produce a *vic*-glycol group.

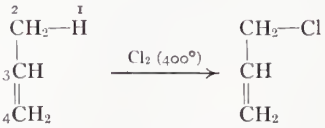


Shell process



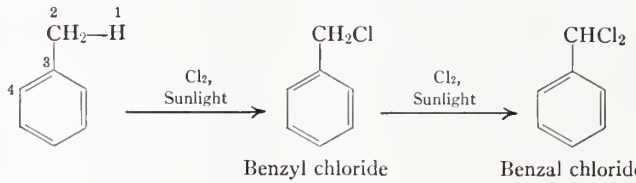
11.17——— The first step in the Shell process for production of glycerol can be described as an allylic substitution. An allylic hydrogen, which

Allylic chlorination

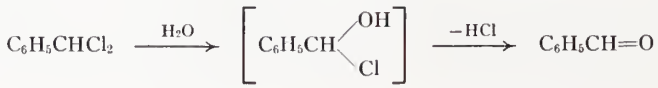


occupies position 1 and is therefore activated by the 3,4-double bond, is replaced by chlorine. The allylic substitution is effected at a high temperature and is evidently a free-radical reaction. At ordinary temperature chlorine adds to the double bond of propylene, but at 400° substitution is faster than addition.

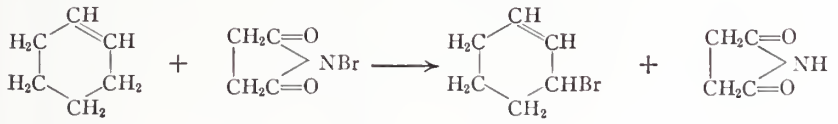
11.18——— **Benzyl Chloride.** — Toluene has an allylic hydrogen activated by the unsaturated ring and can be converted into the allyl-type halide



benzyl chloride. It is necessary to exclude catalysts which promote electrophilic attack of the ring and to expose the hydrocarbon to sunlight during the reaction. Light energy splits chlorine molecules to reactive chlorine radicals, which initiate free-radical substitution of hydrogen (3.3). Since the benzene ring absorbs ultraviolet light, irradiation also enhances the activation effect. Benzyl chloride thus can be prepared in good yield by photochemical chlorination in the side chain. The reaction can also be extended to introduction of two chlorine atoms. The product, benzal chloride, is useful as an intermediate to benzaldehyde, which is formed on hydrolysis:



Allylic Bromination. — In 1924 the German chemist Karl Ziegler discovered that unsaturated compounds can be brominated in the allylic position by reaction with N-bromosuccinimide. For example, cyclohexene (a) affords 3-bromocyclohexene-1: 11.19



(a) N-Bromosuccinimide (b) Succinimide

Use of N-bromosuccinimide

The reaction is catalyzed by peroxides and by light, and hence is a free-radical reaction comparable to the thermal chlorination of propylene discussed above. Allylic bromination with N-bromosuccinimide is particularly useful for conversion of monounsaturated compounds into dienes, and of dienes into trienes. Thus the allylic bromide (b)



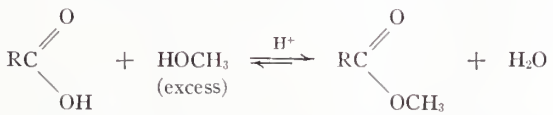
(b) (c)

Synthesis of a diene

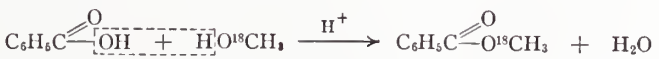
derived from cyclohexene is convertible by dehydrohalogenation into cyclohexadiene-1,3 (c).

ESTERIFICATION AND HYDROLYSIS

In the Fischer method of esterification of an acid, consisting in refluxing the acid with excess alcohol and a trace of mineral acid as catalyst (2.28, 9.5), the water eliminated between the reactants could 11.20



conceivably arise by replacement of either the hydroxyl group of the acid or the hydroxylic hydrogen atom of the acid. Experiments with isotopically labeled reactants have established that when the alcohol involved is primary or secondary the elimination occurs in one direction, and when the alcohol is tertiary it proceeds in the other. When ordinary benzoic acid containing the O^{16}-isotope is esterified with heavy methanol, $CH_3O^{18}H$, in the presence of hydrogen chloride, the water formed has the ordinary isotopic composition, and hence the reaction proceeds as follows:



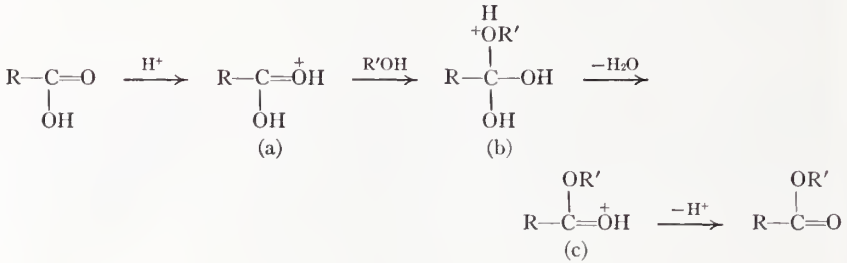
Isotopic label reveals mechanism

The hydroxyl group eliminated thus comes from the acid rather than from the primary alcohol. Similar experiments have shown that

secondary alcohols react in the same way, but that a tertiary alcohol contributes the hydroxyl group of the water molecule formed. The reactions evidently proceed by two different mechanisms.

11.21 In esterifications with primary and secondary alcohols, the reaction rate is dependent upon the concentration of both the acid and alcohol components. The following mechanism accords with this finding and defines the role of the acid catalyst. A proton from the

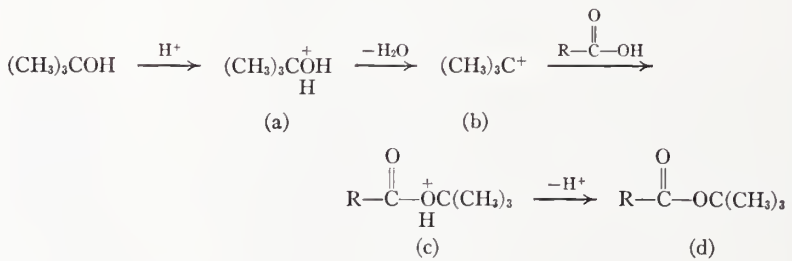
Mechanism of esterification of RCH_2OH and R_2CHOH



mineral acid accepts a pair of unshared electrons from the carbonyl oxygen atom of the organic acid to form an oxonium ion (a); this is attacked by the alcohol to give (b), which loses water to form the oxonium ion (c); loss of a proton then affords the ester. The proton required in the first step is regenerated in the last step. That the proton functions in the sense of a Lewis acid, or electron acceptor, explains why the reaction is also catalyzed effectively by boron fluoride, which is also a powerful electron acceptor (9.27).

11.22 That a tertiary alcohol such as *t*-butyl alcohol loses the whole hydroxyl group rather than just the hydroxylic hydrogen is interpreted to mean that the key intermediate is the carbonium ion (b). In the

Mechanism of esterification of R_3COH



presence of the mineral acid catalyst the alcohol initially combines with a proton to form the oxonium ion (a), which by loss of water affords trimethylcarbonium ion (b), stabilized by the combined electron-releasing power of the three methyl groups. The carbonium ion combines with the acid to form a substituted oxonium ion (c) that expels a proton to form the ester (d). The catalytic role of the proton is accounted for, and the differing behavior of the tertiary alcohol is

interpreted as due to the inductive effect of the three alkyl groups in promoting formation of a carbonium ion.

Hydrolysis of Esters. — Esterification is a reversible reaction, and mineral acids catalyze hydrolysis of esters just as they catalyze their formation. Thus hydrolysis can be accomplished by refluxing an ester with dilute hydrochloric acid or, if the ester is sparingly soluble in water, with aqueous-alcoholic hydrochloric acid. An alternative procedure is to heat the ester with aqueous or aqueous-alcoholic sodium hydroxide. This method is called saponification because as applied to the hydrolysis of esters of fats it produces soap as one product (and glycerol as the other); it has the advantage that the carboxylic acid formed is removed from the equilibrium as the water-

11.23

$$RCOOCH_3 + NaOH \longrightarrow RCOO^-Na^+ + CH_3OH$$

Saponification

soluble sodium salt. When hydrolysis of the ester is complete, acidification of the alkaline solution liberates the free acid.

Hydrolysis of Alkylsulfuric Acids. — Ethylsulfuric acid, resulting either from reaction of ethanol with concentrated sulfuric acid in the cold or by addition of the acid to ethylene, is an ester. It can be

11.24

$$CH_3CH_2OSO_2OH + H_2O \text{ (excess)} \longrightarrow CH_3CH_2OH + H_2SO_4$$

$$\uparrow\ 0\text{–}15^\circ$$

$$CH_2{=}CH_2 + H_2SO_4$$

hydrolyzed readily and is a sufficiently strong acid to catalyze the reaction. Thus one of the methods by which ethanol is produced utilizes ethylene derived from cracking; the gas is absorbed in concentrated sulfuric acid and the ester hydrolyzed by suitable dilution with water. The overall result of addition and hydrolysis is hydration of the double bond; alkynes can be hydrated in one step, but alkenes require two steps. The reaction is generally applicable and the structure of the alcohol is predictable from the Markownikoff rule. Thus

Alcohols by indirect hydration of alkenes

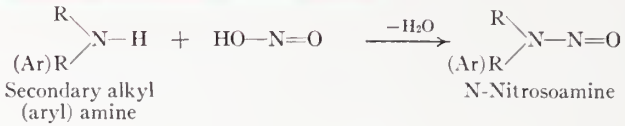
$$CH_3CH{=}CH_2 \xrightarrow{HOSO_2OH} CH_3\underset{\displaystyle OSO_2OH}{\underset{|}{C}}HCH_3 \xrightarrow{H_2O} CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$$

propylene, from cracking, yields isopropyl alcohol. *sec*-Butyl alcohol is made from the mixture of butene-1 and butene-2 present in the C_4-cut of cracked gasoline; both isomers yield the same product.

$$\left.\begin{array}{l} CH_3CH_2CH{=}CH_2 \\ \text{Butene-1} \\ CH_3CH{=}CHCH_3 \\ \text{Butene-2} \end{array}\right\} \xrightarrow{H_2SO_4} CH_3CH_2\underset{\displaystyle OSO_2OH}{\underset{|}{C}}HCH_3 \xrightarrow{H_2O} CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$$

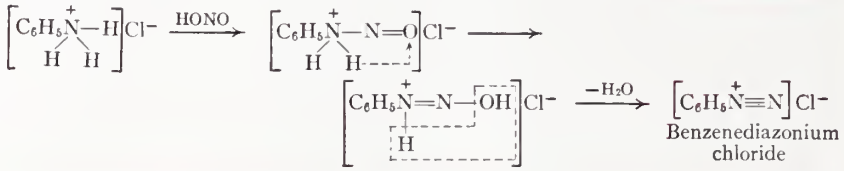
sec-Butyl alcohol

11.25 Secondary amines react with nitrous acid by elimination of water and formation of N-nitroso compounds. A similar reaction probably



occurs as the first step in the formation from aniline hydrochloride of the remarkable salt benzenediazonium chloride. In this compound

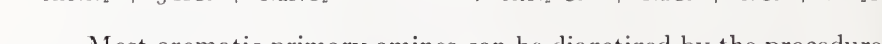
Mechanism of formation



penta- and trivalent nitrogen atoms are connected by a triple bond, which may arise by a 2,4-hydrogen shift in the transient N-nitroso compound, followed by dehydration. Benzenediazonium chloride is an ionic salt very soluble in water and insoluble in ether; in aqueous solution it is completely dissociated.

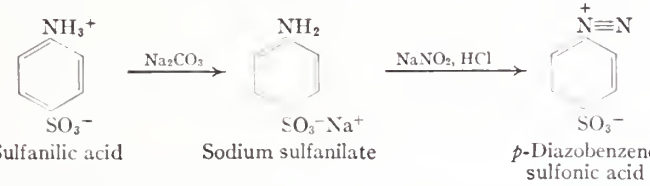
11.26 Benzenediazonium chloride is very reactive and enters into some useful replacements. It is also sensitive and easily decomposed, but the salt is stable in dilute mineral acid solution at low temperatures and can be prepared easily in such a solution at 0° by the process of diazotization, conducted as follows. The amine is dissolved in a suitable volume of water containing three equivalents of hydrochloric acid, by heating if required, and the solution is cooled well in ice, when the amine hydrochloride usually crystallizes. With control of the temperature to 0–5°, an aqueous solution of sodium nitrite is added in portions until, after allowing a few minutes for reaction, the solution gives a positive test for excess nitrous acid with starch–iodide paper. The amine hydrochloride dissolves in the process to give a clear solution of the much more soluble diazonium salt. One equivalent of hydrochloric acid is bound by the amine and provides the anion of the product, a second reacts with sodium nitrite to liberate nitrous acid, and the third maintains proper acidity required to stabilize the diazonium salt by inhibition of secondary changes. The process can be summarized as follows:

Diazotization in aqueous solution



11.27 Most aromatic primary amines can be diazotized by the procedure indicated. Usually a clear colorless solution of the diazonium salt

results, even though the amine salt used is only sparingly soluble, but in some instances the diazonium salt crystallizes. This is the case with sulfanilic acid because of the formation of an inner salt. The substance is diazotized by bringing it into solution as the sodium salt, adding the requisite amount of sodium nitrite, and pouring the solution on a mixture of ice and concentrated hydrochloric acid; nitrous acid and the dipolar sulfanilic acid are liberated together and promptly interact, and after a few seconds the dipolar diazonium salt separates:



Sulfanilic acid — Sodium sulfanilate — *p*-Diazobenzenesulfonic acid

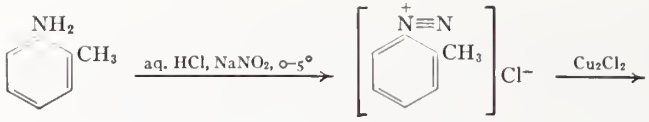
Diazotized sulfanilic acid

Hydrolysis to Phenols. — When a solution of a diazonium salt in aqueous sulfuric acid is boiled, nitrogen is evolved and the amine derivative is converted into the corresponding phenol. The crude re- 11.28

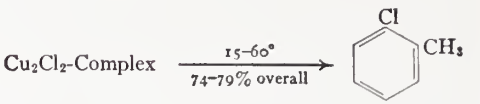
$$[ArN{\equiv}N]Cl + HOH \longrightarrow ArOH + N_2 + HCl$$

action product may be deeply colored, but purification can be accomplished by extraction with alkali or by steam distillation, and the pure phenol obtained in moderate yields. Since the diazonium salt need not be isolated, introduction of a hydroxyl group can be accomplished in essentially three steps: nitration, reduction to the amine, and diazotization in aqueous medium followed by hydrolysis in the same solution.

Sandmeyer Reaction. — This reaction permits replacement of the amino group, through the diazonium salt group, by chlorine, bromine, or iodine atoms, or by the nitrile group. The discoverer, Traugott Sandmeyer, was assistant to Victor Meyer at Heidelberg. When a solution of one equivalent of cuprous chloride in hydrochloric acid is added to a solution of a diazonium salt a deep brown, sparingly soluble complex separates consisting of a double molecule of the diazonium salt and cuprous chloride, and when the suspension of this substance is warmed, decomposition sets in with evolution of nitrogen, disappearance of the solid, and separation of an oily layer containing the organic halide. Although the crude reaction mixture usually is dark colored, separation of the halide from contaminants and inorganic salts can be accomplished by steam distillation. Both *o*- and *p*-chlorotoluene can be prepared in good yield; this method also is convenient for obtaining *m*-nitrochlorobenzene free from isomers, since pure *m*-nitroaniline is available by partial reduction of *m*-dinitrobenzene. For preparation of a bromide by the Sandmeyer reaction, 11.29



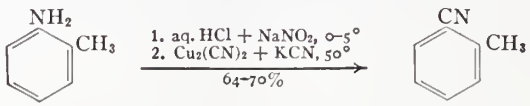
Replacement by halogen



o-Chlorotoluene

the amine is diazotized in sulfuric acid solution and the resulting aryldiazonium sulfate treated with a solution of cuprous bromide in excess hydrobromic acid; the complex is then decomposed by heat. *p*-Bromotoluene can be prepared from *p*-toluidine in 70–73% yield, and *o*-chlorobromobenzene is obtainable from *o*-chloroaniline with equal success. The reaction can be applied to preparation of nitriles, which result from the action of a solution of cuprous cyanide in excess potassium cyanide on a diazonium salt, as shown in the example.

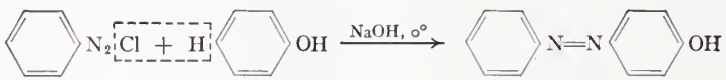
Replacement by CN



o-Tolunitrile
(b.p. 205°)

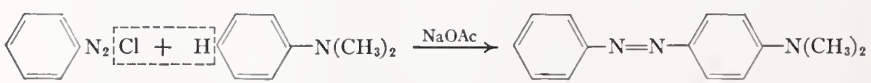
11.30 Coupling Reaction. — Diazonium salts react readily with phenols and aryl amines to form bright-colored azo compounds in which the two aromatic nuclei are linked through the azo grouping, —N=N—. The smoothly proceeding reaction is described as coupling. Benzenediazonium chloride couples with phenol in alkaline solution rapidly at ice-bath temperature to form *p*-hydroxyazobenzene. The proper

Azo compounds



p-Hydroxyazobenzene
(orange, m.p. 152°)

procedure is to stir the solution of benzenediazonium chloride slowly into a chilled solution of phenol containing sufficient alkali to neutralize the organic and inorganic acids in the resulting mixture and maintain suitable alkalinity. Dimethylaniline couples analogously in an aqueous medium that is either neutral or weakly acidified with acetic acid, and gives a yellow *p*-benzeneazo compound. These ex-

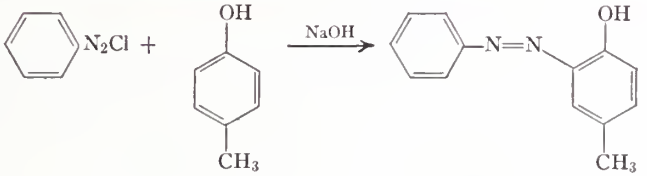


p-Dimethylaminoazobenzene
(yellow, m.p. 117°)

amples illustrate a reaction that is specific to phenols and to tertiary amines having available a free position *ortho* or *para* to the hydroxyl or amino group. Where a choice is open, coupling occurs practically exclusively in the *para* position. Coupling occurs readily enough in the *ortho* position if this alone is available. The coupling reaction is

Replacement Reactions

para-Coupling preferred but ortho possible



p-Cresol

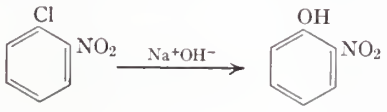
Benzeneazo-*p*-cresol
(yellow, m.p. 108°)

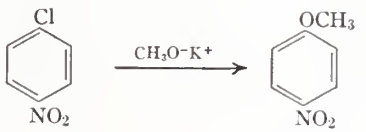
spectacular because of the rapid formation of brightly colored products from colorless components.

NUCLEOPHILIC DISPLACEMENT

Both *o*- and *p*-nitrochlorobenzene show an enhanced reactivity of the chlorine atom evidently due to the effect of the nitro group in the *ortho* or *para* position. Thus *o*-nitrochlorobenzene reacts with

11.31





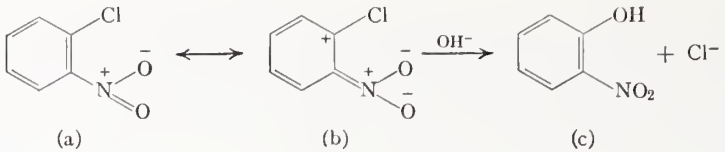
p-Nitroanisole

Labilization by o- or p-NO_2

alkali, or even with sodium carbonate solution at 130°, with displacement of halogen and formation of *o*-nitrophenol. The *p*-isomer similarly reacts with potassium methoxide to give the methyl ether formulated. Chlorobenzene, under the same conditions, is inert, and so is *m*-nitrochlorobenzene. A nitro group in the ring thus can exert a labilizing effect on the halogen atom only if it is *ortho* or *para* to the halogen. The labilization is manifested only to a specific type of attacking agent typified by the hydroxide ion in one example and the methoxide ion in the other. These agents are negatively charged ions, or nucleophiles, and hence an *o*- or *p*-nitro group enhances susceptibility to nucleophilic displacement. The phenomenon can be accounted for as a consequence of resonance. One of the resonance structures of *o*-nitrochlorobenzene (a) can be represented as in (b),

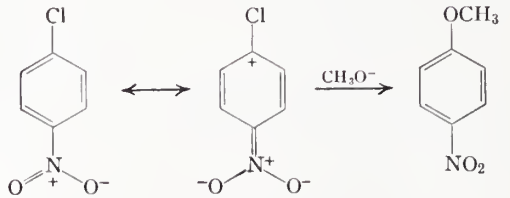
Not m-NO_2

Consequence of resonance



(a) (b) (c)

in which a positive charge is distributed onto the carbon atom carrying the chlorine atom. This positive atom is thus an attractive site for attack by the negative hydroxide ion, and such attack results in displacement of chlorine by hydroxyl and separation of chloride ion. A *p*-nitro group (d) similarly gives rise to a resonance structure (e)

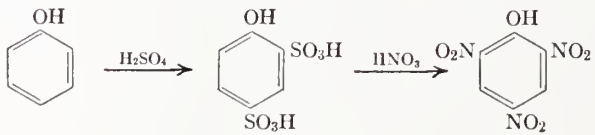


(d) (e) (f)

with a positive charge on the *para* carbon atom inviting nucleophilic displacement. If the nitro group is in the *meta* position, no comparable resonance structures can exist and no labilizing effect is noted.

11.32 A practical consequence of the labilizing effect of nitro groups is illustrated by the evolution of the present process for the manufacture of picric acid for use as a high explosive. In the early process picric acid was made by sulfonation of phenol followed by nitration.

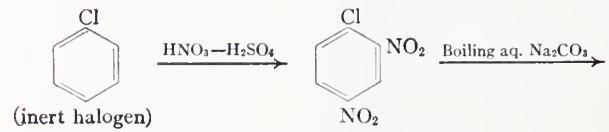
Old picric acid process



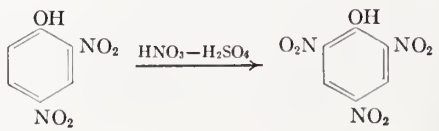
Picric acid

Phenol is now made from chlorobenzene in a reaction requiring high temperature and pressure because of the inert character of the halogen. In the modern picric acid process the requirement of drastic conditions for effecting nucleophilic displacement is eliminated by conversion of chlorobenzene into the 2,4-dinitro derivative, in which the halogen is

Modern process



(inert halogen) (labile halogen)



iabilized by the combined effect of two *op*-nitro groups. The displacement is thus conducted at a stage where it proceeds under very mild conditions. The hydroxyl group formed then facilitates introduction of the third nitro group.

SUMMARY

Alkyl Halides and Alcohols

Replacement of X in RX. Williamson ether synthesis: $RI + NaOR' \longrightarrow ROR'$. Preparation of alcohols: $RI + AgOH \longrightarrow ROH + AgI$. Formation of a Grignard reagent: RI (Br, Cl) + Mg (in ether) $\longrightarrow$ RMgI (alkylmagnesium iodide). Reaction with water $\longrightarrow CH_4$. Liberation of methane by other compounds with active hydrogen: ROH, RCO_2H, RNH_2, R_2NH. Zerewitinoff determination.

Hydrolysis of alkyl halides with alkali in dilute water–alcohol useful in kinetic studies (reaction rates under varying conditions).

Order of alkyl reactivity: CH_3X 5–20 times as reactive as CH_3CH_2X; ethyl and higher homologs all about the same. Order of halide reactivity: RI > RBr > RCl > RF (same order for the aryl halides).

Mechanism of hydrolysis. The hydrolysis $CH_3Br + OH^- \longrightarrow CH_3OH$, defined as nucleophilic substitution (S_N), is bimolecular (2nd order, S_N2). Postulate of back-side attack by OH^- to produce transition complex. Electron-release of methyl explains decreased reactivity of CH_3CH_2Br and $(CH_3)_2CHBr$. Inductive effect of three methyls inhibits bimolecular hydrolysis of $(CH_3)_3CBr$, and hydrolysis is unimolecular or first-order (S_N1); rate-controlling step is formation of $(CH_3)_3C^+$.

Allyl-type halides very reactive. In $CH_2{=}CH{-}CH_2Br$, Br in position 1 is activated by the 3,4-double bond. Reaction is unimolecular. S_N1 mechanism: separation of Br^- in the rate-controlling step gives a carbonium ion stabilized by resonance and this stabilization promotes the hydrolysis. Benzyl chloride, $C_6H_5CH_2Cl$, is of the allyl type and highly reactive; here the *op*-positions in the ring participate in the resonance effect.

Vinyl-type halides very inert. No Grignard reagent from $CH_2{=}CHBr$ or from chlorobenzene. Inertness of vinyl halides attributed to resonance:

$$CH_2{=}CH{-}Br \longleftrightarrow \bar{C}H_2{-}CH{=}Br^+$$

The C—Br link has some double-bond character and is hence shortened and stabilized.

Alkyl halides from alcohols. For preparation of bromides and iodides: $ROH + HX \longrightarrow RX + H_2O$. Hydrochloric acid is less reactive and alkyl chlorides usually must be made thus: $3\,ROH + PCl_3 \longrightarrow 3\,RCl + P(OH)_3$. Exceptions: *t*-butyl alcohol and allyl alcohol react readily with hydrochloric acid to form the chlorides. Both reactions are S_N1 and involve formation of carbonium ions. The ion from *t*-butyl alcohol is stabilized by the three methyl groups, that from allyl alcohol by resonance.

Allylic Substitution

Glycerol from petroleum. Glycerol, a by-product of manufacture of soap, required in quantity in time of war for production of nitroglycerin, the trinitrate ester. Nitroglycerin a liquid highly sensitive to shock. Discoveries by Nobel: (1) nitroglycerin absorbed in porous earth gives the practical explosive dynamite; (2) guncotton (cellulose trinitrate) is gelatinized by nitroglycerin to form an explosive jelly now used to make propellant for shells.

Shell Oil Company process based on thermal chlorination of propylene to allyl chloride: $CH_2{=}CH{-}CH_2{-}H \longrightarrow CH_2{=}CHCH_2Cl$. Substitution in the allylic position activated by 3,4-double bond. The free-radical substitution takes precedence over addition to the double bond because addition product is unstable at 400°. Remaining steps: hydrolysis to allyl alcohol, addition of HOCl, elimination of HCl to form an oxide, hydrolysis to glycerol.

Photochemical chlorination with exclusion of catalysts: $C_6H_5CH_2{-}H$ (activated, allylic) $\longrightarrow$ $C_6H_5CH_2Cl$ (benzyl chloride) $\longrightarrow$ $C_6H_5CHCl_2$ (benzal chloride; is hydrolyzed to benzaldehyde). Free-radical reaction.

Allylic bromination. (Ziegler): $-CH{=}CHCH_2- \longrightarrow -CH{=}CHCHBr-$. A free-radical reaction utilizing as reagent N-bromosuccinimide. Useful for preparation of conjugated systems, e.g. $-CH{=}CHCH_2CH_2- \longrightarrow -CH{=}CHCHBrCH_2- \longrightarrow -CH{=}CHCH{=}CH-$.

Esterification and Hydrolysis

Fischer esterification of an acid with excess methanol and catalyst (HCl, H_2SO_4, BF_3-etherate). Esterification of C_6H_5COOH with $CH_3O^{18}H$ proves that hydroxyl group eliminated comes from the acid, not the alcohol. The same is true for secondary alcohols, but with a tertiary alcohol the OH comes from the alcohol and hence the reaction proceeds by a different mechanism.

Mechanism of esterification of primary and secondary alcohols (S_N2): combination of the acid with a proton to form an oxonium ion; reaction with R'OH with expulsion of water (R'OH becomes attached to carbon, accepts the positive charge; expulsion of proton. Catalytic function of proton served equally well by other electron acceptors (Lewis acids), e.g. BF_3. Esterification of tertiary alcohol involves formation of carbonium ion, R_3C^+ (inductive effect of three alkyl groups), and hence elimination of the hydroxyl group from the alcohol rather than the acid.

Hydrolysis of esters, e.g. $RCOOCH_3$, is the reverse of esterification and can be done by refluxing with dilute HCl. Alkaline hydrolysis, saponification, is more efficient because the acid component is removed from the equilibrium by salt formation.

Hydrolysis of the ester $ROSO_2OH$ to ROH useful in preparation of alcohols. Thus an alkene adds sulfuric acid to form an alkylsulfuric acid, which on hydrolysis yields the alcohol. Propylene (by cracking) $\longrightarrow$ isopropyl alcohol. Butene-1 and butene-2, components of a cracking fraction, both yield *sec*-butyl alcohol.

Diazonium Salts

Aniline hydrochloride, $C_6H_5N^+H_3Cl^-$, reacts with nitrous acid to form benzenediazonium chloride, $[C_6H_5N^+{\equiv}N]Cl^-$. Possible mechanism based on reaction of secondary amines: $R_2NH + HON{=}O \longrightarrow R_2N{-}N{=}O$ (nitrosoamine). The diazonium salt is ionic and very reactive. Is easily formed in aqueous solution at 0° by diazotization of an amine: $ArNH_2$ in water + 3 moles HCl, cool in ice, add $NaNO_2$. Diazotization of sulfanilic acid to *p*-diazobenzenesulfonic acid.

Hydrolysis to phenols by refluxing with 45% H_2SO_4: $ArN_2^+Cl^- + H_2O \longrightarrow ArOH + N_2 + HCl$.

Sandmeyer reaction: $ArN_2^+Cl^- + Cu_2Cl_2 \longrightarrow$ complex $\longrightarrow ArCl + N_2$. With Cu_2Br_2 the product is ArBr; with $Cu_2(CN)_2$ it is ArCN.

Diazo coupling.

$$C_6H_5N_2^+Cl^- + C_6H_5OH\ (NaOH,\ 0°) \longrightarrow C_6H_5N{=}NC_6H_5OH\text{-}p$$

Reaction rapid at 0°; exclusive *p*-substitution; highly colored product. N,N-Dimethylaniline couples similarly in neutral or weakly acid solution. Coupling occurs in *o*-position if *p*-position is blocked (*p*-cresol).

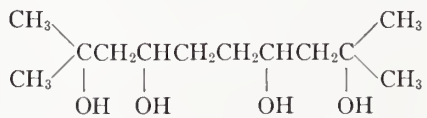
Nucleophilic Displacements

Chlorine atoms of *o*- and *p*-nitrochlorobenzene show enhanced reactivity: dilute NaOH displaces chlorine by OH, $KOCH_3$ displaces chlorine by OCH_3. Under same conditions chlorobenzene and *m*-nitrochlorobenzene are inert. Displacement by a nucleophile (OH^-, CH_3O^-) attributed to resonance structure with a positive charge on carbon carrying the chlorine; the positive site attractive for attack by the nucleophile.

Practical use: production of picric acid from chlorobenzene by dinitration to labilize the chlorine, displacement by OH, and further nitration.

PROBLEMS

1. What reagents would you choose for effecting each of the following transformations:
   (*a*) $(CH_3)_2CHCH_2I \longrightarrow (CH_3)_2CHCH_2OCH_3$
   (*b*) $(CH_3)_3CCH_2I \longrightarrow (CH_3)_3CCH_2OH$
   (*c*) $(CH_3CH_2)_3COH \longrightarrow (CH_3CH_2)_3CCl$
   (*d*) $C_6H_5CH{=}CHCH_2OH \longrightarrow C_6H_5CH{=}CHCH_2Cl$
   (*e*) $CH_3CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH_2CH_2Cl$
2. How could evidence be obtained that the following compound has two secondary and two tertiary alcoholic groups?

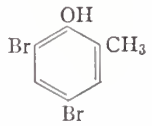


3. Allyl bromide reacts with potassium acetate as follows:

$$CH_2{=}CHCH_2Br + KOCOCH_3 \longrightarrow CH_2{=}CHCH_2OCOCH_3$$

Cinnamyl bromide, $C_6H_5CH{=}CHCH_2Br$, on reaction with potassium acetate gives two

isomeric products. Suggest a mechanism for the reaction and structures for the two products.

4. The high-temperature chlorination of propylene to allyl chloride (11.16) is one illustration of the fact that high temperatures favor formation of unsaturated compounds. Several other examples of the phenomena have been cited in earlier chapters. See how many you can recall.
5. Note the structure and ultraviolet absorption maximum of vitamin A (or A_1, 5.14). This substance occurs in halibut liver oil and in most marine fish oils. Fresh-water fish oils contain a companion substance, vitamin A_2, which is similar in chemical behavior but which is distinguished by a markedly shifted absorption maximum, λ_{max} 351 mμ. The structure was established by synthesis, and A_2 is now known to have the same skeletal structure as A_1 and to have two hydrogen atoms less than A_1. From this information you should be able to deduce the structure of A_2 and to suggest a method for its synthesis from A_1.
6. By what steps could you effect each of the following transformations:
   (*a*) *p*-Nitroaniline ⟶ *p*-chlorobromobenzene (BrC_6H_4Cl-*p*).
   (*b*) *p*-Toluidine ⟶ terephthalic acid ($HO_2CC_6H_4CO_2H$-*p*).
   (*c*) *o*-Toluidine ⟶ 

   (2,4-dibromo-*o*-cresol)
7. Suggest a method of preparing 2,4-diamino-*N*-methylaniline, starting with chlorobenzene.

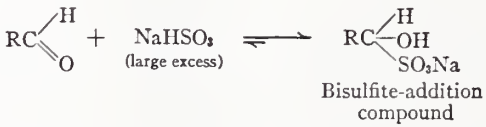
CHAPTER 12

REACTIONS OF CARBONYL COMPOUNDS

ADDITION REACTIONS

12.1 It has been noted (4.25) that catalytic hydrogenation is the only instance of addition of the same reagent to both carbon–carbon and carbon–oxygen double bonds. The typical reagents that add to alkenes do not add to carbonyl compounds, and the typical carbonyl reagents to be discussed in this chapter do not add to alkenes.

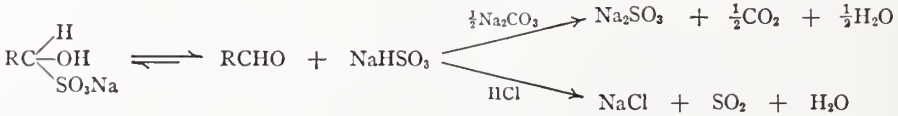
12.2 **Addition of Sodium Bisulfite.** — A reaction characteristic of aldehydes and of some ketones is addition of sodium bisulfite, employed in a saturated (40%) aqueous solution. Equilibrium is reached, but the carbonyl component can be converted almost entirely into the



Bisulfite-addition compound

addition product by use of excess bisulfite. The addition product is a crystalline salt and has the usual characteristics of an ionic compound; it is very soluble in water but subject to salting out by the common-ion effect, and it is insoluble in ether, infusible, and nonvolatile. Since the reaction is reversible, the aldehyde can be regenerated by adding to an aqueous solution of the product an amount of sodium carbonate or hydrochloric acid sufficient either to neutralize or to destroy the free sodium bisulfite present in equilibrium. Because of their specific physical properties and ease of formation and decom-

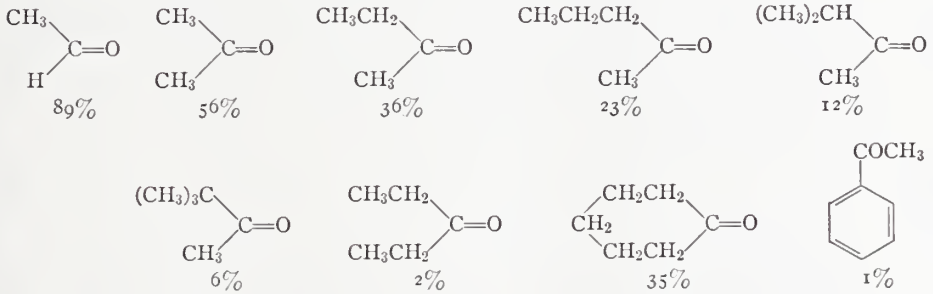
A reversible reaction useful in purification



position, bisulfite-addition products are useful for separation and purification of carbonyl compounds. To separate an aldehyde from an alcohol, for example, the mixture is shaken with excess saturated sodium bisulfite solution to form and to salt out the addition product; this is collected as a white solid and washed with bisulfite solution, ethanol, and then ether, to eliminate all traces of the original alcohol; the dried solid is dissolved in water and treated with sodium carbonate or hydrochloric acid; the liberated aldehyde is precipitated or obtained by distillation or by extraction with ether.

The relative additive power of carbonyl compounds is shown by figures for the amount of addition product formed in one hour with just one equivalent of sodium bisulfite. That acetone adds to a

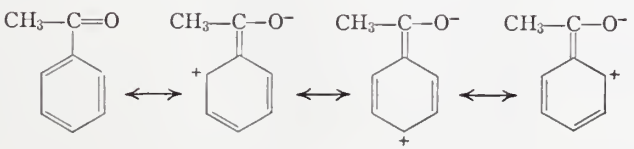
12.3



Extent of reaction with 1 equiv. of $NaHSO_3$ in 1 hr.

lesser extent than acetaldehyde can be attributed to the greater steric hindrance of two methyl groups, as compared to one methyl group and one hydrogen atom. The larger the two groups attached to carbon, the greater is the impediment to approach of the reagent. In the series of ketones having one methyl group, the extent of blocking increases as the second group is enlarged from methyl to ethyl to *n*-propyl. The branched groups isopropyl and *t*-butyl exert considerable hindrance to the addition. The reaction is practically stopped if both groups are larger than methyl, as shown by the behavior of diethyl ketone. Cyclohexanone can be regarded as derived from diethyl ketone by insertion of a methylene group to bridge the two C_2-units. The bridge seems to restrict these C_2-units and so to decrease the hindrance which they exert, for cyclohexanone reacts with bisulfite to a considerably greater extent than the noncyclic ketone. The very limited reaction of acetophenone is probably attributable to

Steric hindrance



Acetophenone

Resonance effect

resonance involving the benzene ring; contribution of the resonance structures formulated decreases the double-bond character of the carbonyl group.

12.4 Esters do not form bisulfite addition products and are recognized from this and other facts to be significantly less reactive in additions than aldehydes and ketones. The relationship again seems attributable to a resonance effect. Charge separation in the ester (a) in the

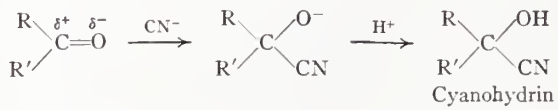
Resonance in esters



direction shown in structure (b) decreases the double-bond character of the carbonyl group and so reduces additive ability.

12.5 **Hydrogen Cyanide Addition.** — The reaction of hydrogen cyanide with the carbonyl group of aldehydes and ketones has been mentioned briefly (3.20) and described as proceeding by nucleophilic attack by CN^- at the positively polarized carbon atom:

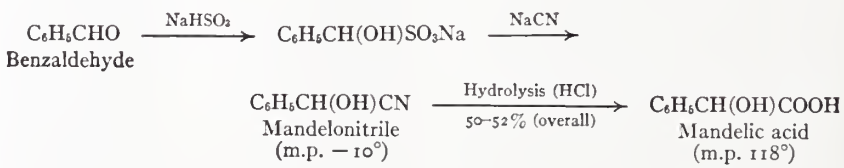
Nucleophilic addition



The scope of the reaction is about the same as that for addition of bisulfite. The carbonyl group of an ester is indifferent to hydrogen cyanide.

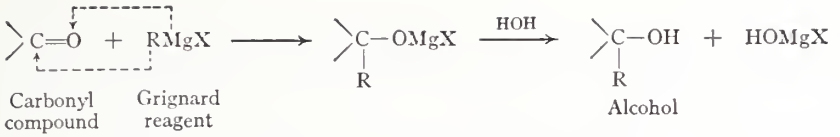
12.6 Since hydrogen cyanide is volatile and highly toxic, advantage is usually taken of a procedure in which the reagent is merely generated as it is used. For example, in the synthesis of mandelic acid by preparation and hydrolysis of the cyanohydrin, benzaldehyde is converted into its bisulfite-addition compound and this is treated with sodium cyanide. Sodium cyanide acts as a base and neutralizes the sodium

Synthesis of an α-hydroxy acid

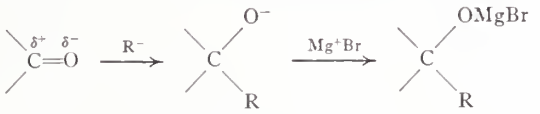


bisulfite in equilibrium with the bisulfite compound with formation of sodium sulfite; the simultaneously liberated aldehyde and hydrogen cyanide then combine to give the cyanohydrin.

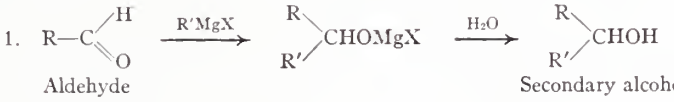
12.7 **Grignard Reaction.** — The key step in a number of useful applications of the Grignard reaction consists in addition of an alkylmagnesium halide to the carbonyl group of a second component, followed by hydrolysis:



The carbonyl component is thereby converted into an alcohol of structure determined by the structures of the two reactants. The reaction doubtless follows the course of hydrogen cyanide addition and initiates in attack by the nucleophilic ion of $R^{-}Mg^{+}Br$:

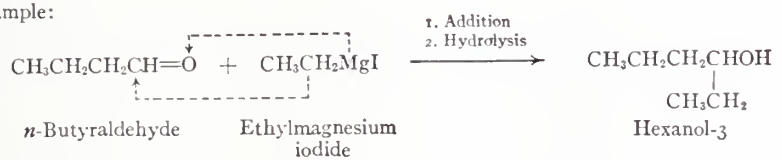


With an aldehyde, which has one alkyl group initially joined to the carbonyl function, the Grignard addition results in a secondary alco-

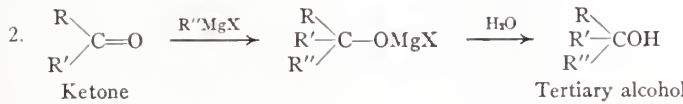


Example:

Aldehydes

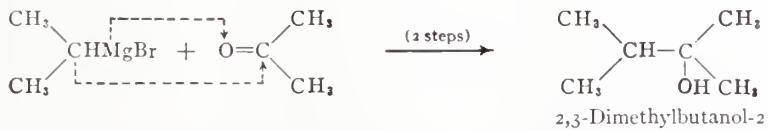


hol (1). A ketone, which has two alkyl groups initially joined to the carbonyl group, is converted into a tertiary alcohol (2).



Example:

Ketones

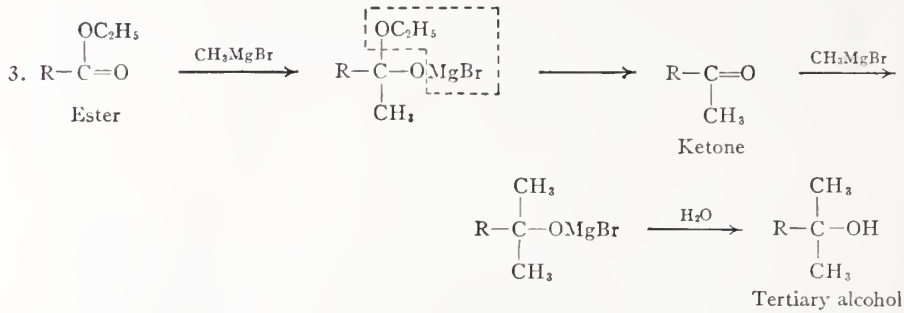


12.8

A Grignard reagent has considerably more power to add to the carbonyl group than sodium bisulfite or hydrogen cyanide, and very few aldehydes or ketones fail to undergo addition. Even esters react, although they do so less easily than ketones for the reason noted above: resonance involving polarization of the ether oxygen detracts from the positive polarization of the carbonyl carbon. The reaction



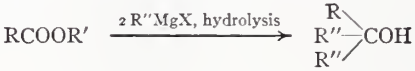
involves initial addition to the carbonyl group of the ester to give an intermediate which has two oxygen substituents on the same carbon and which is no more stable than a corresponding *gem*-diol. If, for example, a methyl Grignard reagent acts on an ethyl ester (3), an



Esters

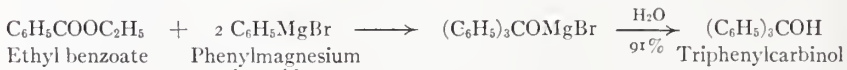
unstable addition product is formed and at once decomposes with elimination of C_2H_5OMgBr and formation of a ketone; this substance then adds a further molecule of Grignard reagent and affords, after hydrolysis, a tertiary alcohol. Since the intermediate ketone is more reactive than the ester starting material, it is not feasible to synthesize a ketone by the reaction of an ester with just one equivalent of Grignard reagent; such a reaction leads merely to a mixture of ester, ketone, and tertiary alcohol.

12.9 Whereas in the synthesis from ketones tertiary alcohols having three different constituents can be prepared, the synthesis from esters can be applied only to the preparation of products in which two of the three alkyl groups are identical. The alcohol cited above as an ex-



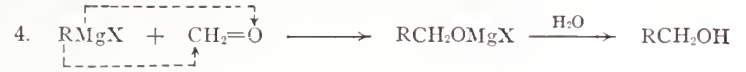
ample in reaction 2 can be prepared alternately by the action of two equivalents of methylmagnesium bromide on methyl isobutyrate, $(CH_3)_2CHCOOCH_3$. The ester method is also useful for the synthesis of alcohols having three identical groups, R_3COH or Ar_3COH. These are usually named as derivatives of the simplest carbon-alcohol or carbinol. Thus $(CH_3)_3COH$ is trimethylcarbinol, and $(C_6H_5)_3COH$ is triphenylcarbinol. Triphenylcarbinol is obtainable in good yield by Grignard reaction of ethyl benzoate with phenylmagnesium bromide.

Synthesis of Ar_3COH

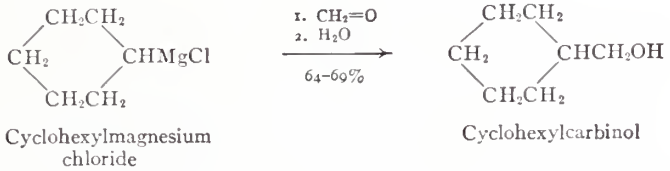


12.10 Synthesis of a primary alcohol by the Grignard reaction can be accomplished by employing a carbonyl component having no attached

alkyl substituents, namely formaldehyde, HCH=O. The type reaction (4) is generally applicable, and increases the carbon chain by one unit. A reagent that also gives primary alcohols, and with



Example:



Cyclohexylmagnesium chloride

Cyclohexylcarbinol

Primary alcohols from formaldehyde

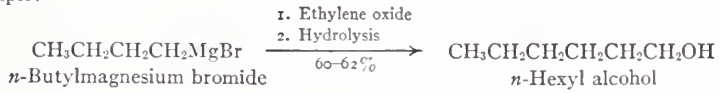
which the chain is lengthened by two carbon atoms, is ethylene oxide. This substance possesses reactivity akin to that of formaldehyde, for the three-membered ring tends to open with ease comparable to that noted for the carbonyl group. In the reaction with a Grignard reagent (5) the oxide ring is ruptured and the alkyl group adds to carbon and the magnesium halide group adds to oxygen.



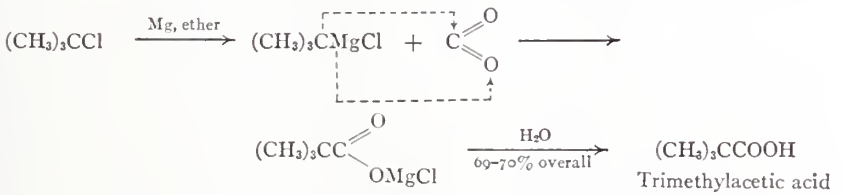
Ethylene oxide

From ethylene oxide

Example:

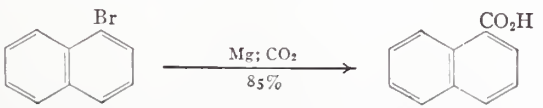


Carbon dioxide has a carbonyl group reactive enough for addition of RMgX, and hence carboxylic acids are obtainable by Grignard synthesis. Carbonation of an alkylmagnesium halide can be accom- 12.11



Grignard synthesis of acids

plished by bubbling carbon dioxide into a solution of the Grignard reagent or by pouring the solution on dry ice. The reaction is applicable in both the aliphatic and the aromatic series.



α-Naphthoic acid

12.12 An acid chloride, like an ester, reacts with a Grignard reagent to give first a ketone and then, with more reagent, a tertiary alcohol. The initial step proceeds more rapidly than the corresponding reaction of an ester, and there is more differentiation between the first and second steps. Consequently ketones can be prepared in reasonable

$$RCOCl \xrightarrow{R'MgX} RCOR' \xrightarrow{R'MgX,\ H_2O} \begin{matrix} R \\ R' \\ R' \end{matrix}\!\!>\!COH$$

yield by using just one equivalent of Grignard reagent and adding it by portions to a solution of the acid chloride (inverse Grignard reaction), in order to avoid exposure of the ketone formed to the action of the reagent.

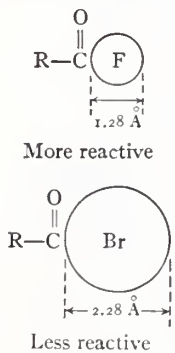
12.13 Formation of a ketone in the reaction of an acyl halide with an organometallic halide could be the result of either direct replacement or initial addition to the carbonyl group and subsequent elimination of a metal dihalide, as follows:

Ketones from acid chlorides

$$R{-}\overset{\displaystyle Cl}{\underset{|}{C}}{=}O + R'MgCl \longrightarrow \left[R{-}\overset{\displaystyle Cl}{\underset{|}{\overset{|}{C}}}{-}O{-}MgCl \right] \longrightarrow R{-}\overset{\displaystyle O}{\underset{R'}{C}} + MgCl_2$$

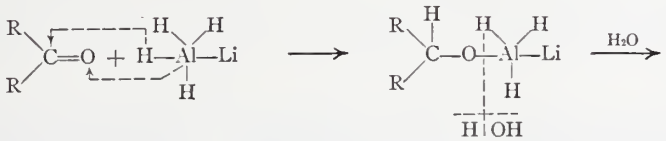
Evidence permitting a decision between the two possibilities is available from a study of the reactivity of a series of acid fluorides, chlorides, and bromides to a given Grignard reagent as evaluated in competitive experiments (J. R. Johnson, Cornell). The order of reactivity is found to be RCOF > RCOCl > RCOBr, which is just the reverse of the order of lability of the carbon–halogen bonds in alkyl halides as determined in replacement reactions: C—Br > C—Cl > C—F. That the acid fluoride is the most, rather than the least, reactive member of the series indicates that the reaction can hardly involve direct severance of the carbon–halogen linkage, and suggests an initial addition to the carbonyl group. The halogen atom then influences the speed of the reaction merely to the extent that it modifies the additive power of the carbonyl group, and this effect may be partly a function of its size, a large atom tending to block free access of the Grignard reagent to the unsaturated center. The relationship between an acid fluoride and an acid bromide is indicated schematically in the margin.

Evidence supporting addition mechanism

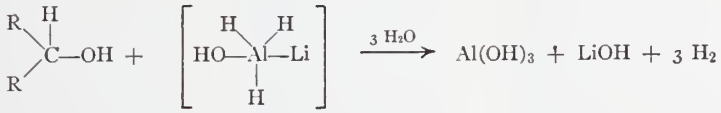


12.14 **Chemical Reduction of the Carbonyl Group.** — Aldehydes and ketones are reducible to alcohols not only by catalytic hydrogenation but also by chemical reducing agents. The same reagents are without effect on alkenes, which are reducible only by the catalytic method. By far the most elegant reagents for reducing carbonyl compounds are metal hydrides of a type discovered in 1947 at the University of

Chicago as an outgrowth of research on the development of the atomic bomb. One is lithium aluminum hydride, $LiAlH_4$. The first step in the reduction of a ketone with this reagent can be represented as an addition. The reaction is conducted in dry ether solution and,



Reduction with lithium aluminum hydride

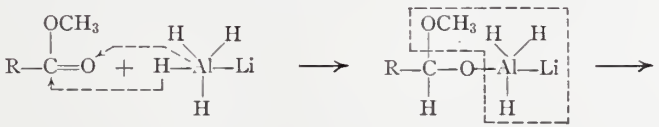


at the end, water is added to hydrolyze the addition product to the alcohol, aluminum hydroxide, and lithium hydroxide. Actually all four hydrogens of the reagent can be utilized, and hence one mole of reagent is able to reduce four moles of an aldehyde or ketone:

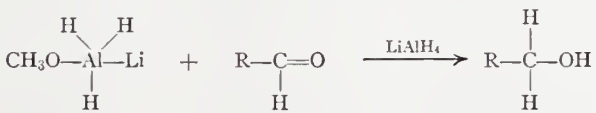


Pure products are obtainable by this method in high yield, and the only limitation is that the reagent is expensive.

Lithium aluminum hydride is also capable of reducing esters, and 12.15
the overall result is: $4\ RCOOCH_3 \xrightarrow{LiAlH_4} 4\ RCH_2OH + 4\ CH_3OH$. The carbonyl group of the ester is thus reduced to a methylene group and the methoxyl group is split off as methanol. The probable mechanism involves addition to the carbonyl group as before, and decomposition of the addition product with formation of an aldehyde,



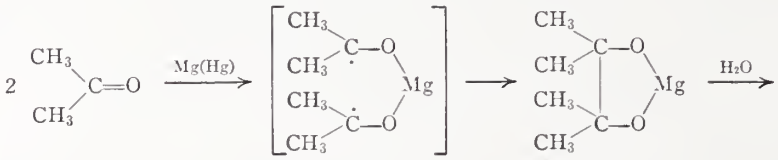
Reduction of an ester



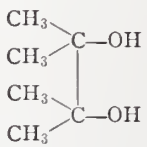
which is then reduced to the alcohol. Free carboxylic acids are reduced similarly.

Bimolecular Reduction. — Reduction of acetone with magnesium 12.16
amalgam in benzene solution follows the normal path of reduction to isopropyl alcohol only in part, but proceeds also by a process described as bimolecular reduction because the product is derived from two

molecules of the starting material. The reaction probably involves attachment of magnesium to the oxygen atoms of two molecules of acetone to form a transient biradical. The two odd electrons then



Preparation of pinacol

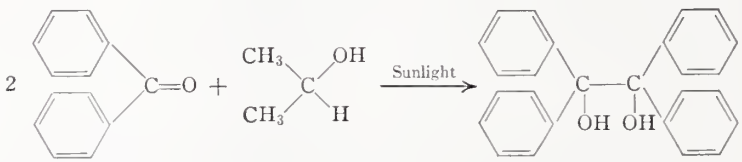


Pinacol

pair up to form magnesium pinacolate, which is subsequently hydrolyzed to pinacol. Pinacol is a liquid, but it forms a crystalline hexahydrate which is easily separated from isopropyl alcohol and excess acetone and isolated in about 50% yield. Most ketones behave similarly, whereas aldehydes usually undergo only normal, unimolecular reduction. The difference appears attributable to the greater availability of the carbonyl group of an aldehyde for simultaneous addition to both carbon and oxygen. In a ketone the carbon is sufficiently hindered by the two alkyl groups to allow opening of the double bond by attack of oxygen alone.

Aldehydes reduced unimolecularly

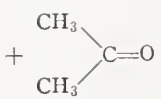
12.17 Benzophenone, $(C_6H_5)_2C{=}O$, undergoes bimolecular reduction in very high yield under photocatalysis. The ketone is colorless, but, since the carbonyl group is conjugated with both unsaturated benzene rings, it absorbs ultraviolet light. The light energy absorbed raises



Benzophenone

Benzopinacol

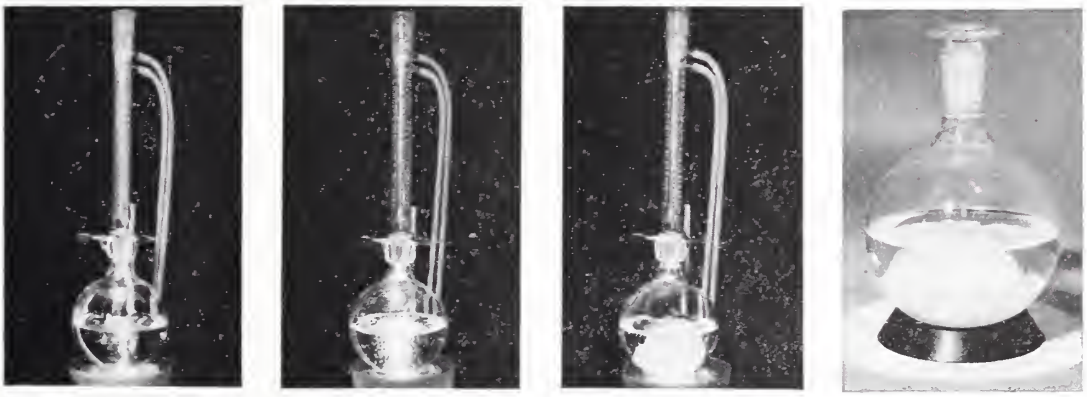
Photochemical hydrogen exchange



the reactivity sufficiently to permit photochemical bimolecular reduction in which isopropyl alcohol serves as hydrogen donor. The products are acetone and benzopinacol. A photographic record of

an experiment shows a solution of 100 g. of benzophenone in 500 ml. of isopropyl alcohol in a flask mounted over an ultraviolet lamp and provided with a reflux condenser (a); the lamp, in producing ultraviolet light, also generates enough heat to boil the isopropyl alcohol (b.p. 82°). After about seven hours, crystals of benzopinacol begin to appear (b) and in twenty-three hours reaction is complete (c); on cooling, further crystals of the sparingly soluble product separate (d); yield 92.5 g.

Four stages in the reaction



(a) (b) (c) (d)

Condensation with Amines. — Among reagents for the carbonyl group are various derivatives of ammonia containing the amino group, $-NH_2$. One reagent, hydroxylamine, represents a combination of the structures of water and of ammonia; and another, hydrazine, is structurally comparable to hydrogen peroxide, to which it bears the same relation as ammonia does to water. These amine

12.18

$$\left.\begin{matrix} H\cdot OH \\ H\cdot NH_2 \end{matrix}\right\} HO\cdot NH_2,\ \text{Hydroxylamine} \qquad HO\cdot OH\{H_2N\cdot NH_2,\ \text{Hydrazine}$$

reagents condense with aldehydes and ketones with elimination of water between the two molecules and formation of an unsaturated nitrogen-containing derivative. The products of condensation with

Type reaction

$$\rangle C{=}O + H_2N{-} \longrightarrow \rangle C{=}N{-}$$

hydroxylamine are oximes, and can be designated as aldoximes or ketoximes, according to the nature of the carbonyl component. The

$$CH_3CH{=}O + H_2NOH \longrightarrow CH_3CH{=}NOH$$

Acetaldoxime (m.p. 47°)

$$(CH_3)_2C{=}O + H_2NOH \longrightarrow (CH_3)_2C{=}NOH$$

Acetoxime (m.p. 60°)

condensations proceed readily on warming the components in aqueous or alcoholic solution, and the examples indicate that oximes are

crystalline solids even though the carbonyl compounds from which they are derived are volatile liquids. The oximes are thus solid derivatives of service for identification.

12.19 Hydrazine reacts in a similar manner to form a hydrazone, but a more useful reagent is phenylhydrazine, $C_6H_5NHNH_2$, discovered by Emil Fischer as a product of the reduction of benzenediazonium chloride with sodium sulfite. The reagent condenses with benzaldehyde, a liquid, to give a crystalline phenylhydrazone suitable for identification by melting point and mixed melting point determina-

Phenylhydrazine

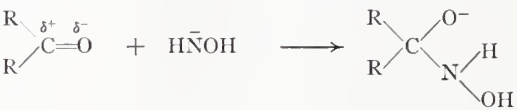
$$\underset{\substack{\text{Benzaldehyde}\\\text{(liquid)}}}{C_6H_5CHO} \xrightarrow{H_2NNHC_6H_5} \underset{\substack{\text{Benzaldehyde phenylhydrazone}\\\text{(m.p. 156°)}}}{C_6H_5CH{=}NNHC_6H_5}$$

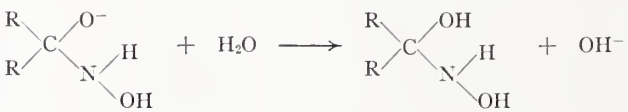
tion. The phenylhydrazone of acetaldehyde is also a crystalline solid, m.p. 99°. Replacement of the oxygen atom of a carbonyl group by the residue $=NNHC_6H_5$ is attended with decided increase in molecular weight and consequent decrease in solubility. Since the reagent reacts with practically all aldehydes and ketones but not with esters or acids, a qualitative test for an aldehyde or ketone consists in addition of phenylhydrazine to an alcoholic solution of the test substance and observation of the separation of a less soluble derivative.

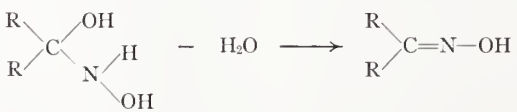
12.20 These condensations appear to involve a step of nucleophilic addition of the type involved in addition of HCN and RMgX. A nucleophile is first produced (a) by abstraction of a proton from the reagent (e.g., hydroxylamine), and then attacks the polarized carbonyl

Nucleophilic reaction of hydroxylamine

(a) $H_2NOH + OH^- \longrightarrow H\bar{N}OH + H_2O$

(b) 

(c) 

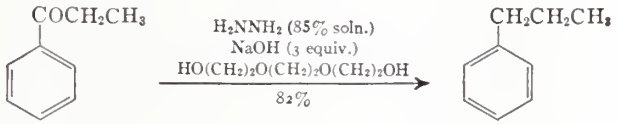
(d) 

in the usual way (b); the ion formed acquires a hydrogen ion from water (c) with regeneration of the hydroxide ion participating in step (a), and elimination of water (d) then gives the unsaturated condensation product. The steps are all reversible, and oximes and phenylhydrazones can be hydrolyzed by boiling with dilute hydrochloric acid with regeneration of the free carbonyl compound.

Wolff-Kishner Reduction. — This method of reduction of a carbonyl group to a methylene group, discovered independently in Germany (Wolff) and in Russia (Kishner), involves formation and pyrolytic decomposition of a hydrazone under basic catalysis. In an 12.21

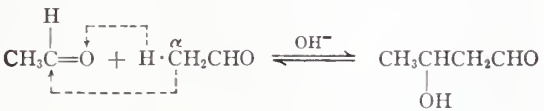


improved procedure (Huang-Minlon, 1946) the carbonyl compound is refluxed briefly in triethylene glycol, a high-boiling, water-miscible solvent, with aqueous hydrazine and sodium hydroxide to form the hydrazone; water is then allowed to distil till the temperature rises to a point favorable for decomposition of the hydrazone (200°); and the mixture is refluxed for several hours to complete the reduction.



Propiophenone — *n*-Propylbenzene

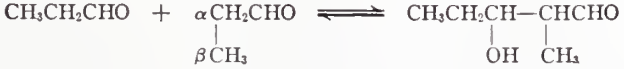
Aldol Condensation. — When a solution of acetaldehyde is treated with a small quantity of sodium hydroxide, two molecules of the substance combine in an equilibrium process and afford aldol, or β-hy- 12.22



Aldol (b.p. 83°/20 mm.)

droxy-*n*-butyraldehyde. The reaction, which is promoted best by bases, involves addition of one molecule of acetaldehyde to the carbonyl group of another molecule, and is dependent upon the activated character of the hydrogen in the α-position to the carbonyl group of the adding molecule. Thus aldol condensation is shown only by aldehydes having at least one hydrogen in the α-position, and not by such substances as trimethylacetaldehyde, $(CH_3)_3CCHO$. Propionaldehyde gives an aldol condensation product by utilization of one of the activated α-hydrogens, and not one of the β-hydrogens:

Requires α-hydrogen



Base-catalyzed aldolization is interpreted as a nucleophilic addition. In an initial, slow step (a) the basic catalyst abstracts a proton from the aldehyde to give the anion required for the more rapid step of addition (b); the terminal step (c) regenerates the catalytic anion. 12.23

Mechanism of nucleophilic addition

(a) $OH^- + HCH_2CHO \rightleftharpoons H_2O + CH_2CHO$

(b) $CH_3CH{=}O + \bar{C}H_2CHO \rightleftharpoons CH_3CHCH_2CHO$ (O⁻)

(c) CH_3CHCH_2CHO (O⁻) $+ H_2O \rightleftharpoons CH_3CHCH_2CHO$ (OH) $+ OH^-$

12.24 Aldol is subject to ready dehydration because of the presence of a β-hydroxyl group adjacent to an activated α-hydrogen atom. Conditions are thus particularly favorable for elimination of water, and aldol is converted into crotonaldehyde either by heating the isolated product alone or with a trace of mineral acid or by merely warming the aqueous solution of the equilibrium mixture resulting from aldol-

$$\underset{\text{Aldol}}{CH_3\overset{\beta}{C}H(OH)-\overset{\alpha}{C}H(H)CHO} \xrightarrow{-H_2O} \underset{\text{Crotonaldehyde}}{CH_3\overset{\beta}{C}H{=}\overset{\alpha}{C}HCHO}$$

ization. Crotonaldehyde is a representative α,β-unsaturated aldehyde available by aldol condensation and dehydration.

12.25 An aromatic aldehyde, such as benzaldehyde, has no α-hydrogen atom available and hence is incapable of self-condensation. Benzaldehyde, however, can supply the acceptor-carbonyl group for aldol condensation with an aliphatic aldehyde. When a mixture of benzaldehyde and acetaldehyde is agitated with aqueous alkali at room temperature, slow condensation occurs with formation of the α,β-unsaturated compound **cinnamaldehyde,** $C_6H_5CH{=}CHCHO$. The

Condensation of an aromatic and an aliphatic aldehyde

$$C_6H_5CHO + CH_3CHO\,[NaOH] \rightleftharpoons \begin{cases} CH_3CHO \rightleftharpoons CH_3CHCH_2CHO\ (OH) \\ [C_6H_5CHCH_2CHO\ (OH)] \xrightarrow{-H_2O} \underset{\substack{\text{Cinnamaldehyde}\\(\text{b.p. } 127^\circ/15 \text{ mm.})}}{C_6H_5CH{=}CHCHO} \end{cases}$$

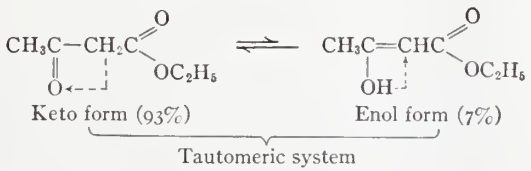
reaction probably involves a reversible aldol addition of acetaldehyde to the carbonyl group of benzaldehyde and an irreversible elimination of water from the addition product; the dehydration is favored by the circumstance that the intermediate has an activated hydrogen atom in an α-position to the carbonyl group and also, on the adjacent carbon atom, a hydroxyl group that is activated by the phenyl group. Acetaldehyde undergoes bimolecular condensation to form aldol, but this reaction is not followed by irreversible dehydration, and the other aldol intermediate thus is utilized for production of cinnamaldehyde. Cinnamaldehyde, a fragrant liquid, occurs as the chief constituent

of oil of cinnamon and oil of cassia and is used in flavoring and in perfumery.

KETO–ENOL TAUTOMERISM

Aldol condensation is one of several reactions that are dependent upon activation by a carbonyl group of an α-hydrogen atom. When a second carbonyl group is present in such a position as to accentuate the activation by the first, the equilibrium may be sufficiently favorable to permit isolation of the enol. The classical example of a compound known in both ketonic and enolic forms is the β-keto ester ethyl acetoacetate, $CH_3COCH_2CO_2C_2H_5$, in which the hydrogens of the methylene group are activated by a carbonyl group on one side and an ester-carbonyl group on the other. Analytical chemical reactions and physical measurements established that ordinary, liquid acetoacetic ester consists of an equilibrium mixture containing approximately 7% of the enol form. The phenomenon of reversible interconversion of isomers is known as tautomerism. A hydrogen atom of the methylene group, activated by the carbonyl group on the one side and the carbethoxyl group on the other, migrates from carbon to oxygen to

12.26



Keto and enol forms of ethyl acetoacetate

give the enol, and since in this substance the hydrogen is also activated, it can migrate back again. The tautomeric migration of hydrogen in either direction is a 2,4-shift. The keto form has been isolated



Interconversion by 2,4-shifts

by cooling a solution of the equilibrium mixture, when the ketonic form eventually separates as a crystalline solid, m.p. $-39°$. The enolic tautomer alone is acidic, and treatment of the mixture with one equivalent of sodium converts all the material into the sodium enolate, $CH_3C(O^+Na^-)=CHCO_2C_2H_5$. The liquid enol has been isolated by passing hydrogen chloride gas into a suspension of the sodio derivative in petroleum ether at $-78°$. At ordinary temperatures each form slowly reverts in part to the other to give the same equilibrium mixture. Equilibrium is established rapidly when either form is treated with a trace of alkali. The position of equilibrium is different in different solvents and varies with temperature.

Other β-keto esters form tautomeric systems of varying enol con-

12.27

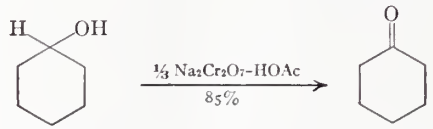
tent; the similarly constituted 1,3-diketones are even more prone to enolize, whereas diesters of the malonic ester type are less enolic, as shown in the following comparison:

Relative enol content

$C_2H_5OOCCH_2COOC_2H_5$	$CH_3COCH_2COOC_2H_5$	$CH_3COCH_2COCH_3$
Diethyl malonate	Ethyl acetoacetate	Acetylacetone
Trace	7%	72%
Enol content of the equilibrium mixture		

Although the methylene group of all three compounds is sufficiently acidic to permit formation of a sodio derivative, the two unsaturated carbethoxyl groups of malonic ester do not provide sufficient activation to stabilize the enol form, whereas acetylacetone, with two unsaturated carbonyl groups, exists largely in the enolic form. Ethyl acetoacetate has a combination of the two unsaturated groups and occupies an intermediate position.

12.28 Oxidation of Ketones. — Cyclohexanol can be oxidized to cyclohexanone with sodium dichromate in acetic acid solution at 60–65° in

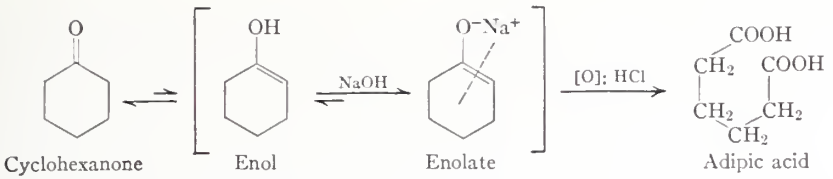


Cyclohexanol — Cyclohexanone

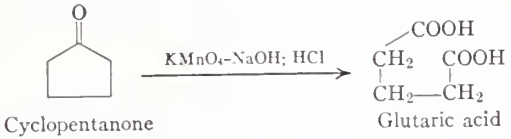
high yield. No precautions are needed to avoid overoxidation, as is the case in the preparation of an aldehyde by oxidation of a primary alcohol, for ketones are stable to dichromate in acid solution. They are also stable to potassium permanganate as long as the solution is not alkaline. Thus when 10 g. of cyclohexanone is shaken at room temperature with a solution of 30.5 g. of potassium permanganate in 250 ml. of distilled water, no reaction occurs. If, however, 5 ml. of 10% sodium hydroxide solution is added, the temperature soon begins to rise and reaches a maximum of 80–82° in 15–20 minutes, with separation of manganese dioxide and eventual discharge of the purple color. After removal of the precipitate by suction filtration, evaporation of the filtrate to a volume of 70 ml. and acidification, the solution on cooling deposits 8 g. of crystals of adipic acid: $HOOCCH_2CH_2CH_2CH_2COOH$. This dibasic acid contains the original six carbon atoms and arises by rupture of the ring. Since the oxidation is catalyzed by alkali, a reagent known to promote enolization, it is probable that the reaction proceeds as follows. The ketone in neutral solution is in equilibrium with an amount of enol too small to be detectable; addition of alkali promotes enolization because the enol is acidic and forms the sodium enolate, which on oxidation is cleaved at the double bond to give, after acidification, adipic acid. Adipic acid is a by-product of

Catalysis by alkali

Intermediate enol



the permanganate oxidation of cyclohexene to the *cis*-diol (4.18) and remains in solution as the sodium salt when the alkaline solution is acidified with carbonic acid. Oxidative cleavage of cyclopentanone



similarly affords a practical route to glutaric acid. Oxidation of open-chain aliphatic ketones is not of preparative use because cleavage can occur in two directions to give mixtures:

$$RCH_2COCH_2R' \xrightarrow{[O]} \begin{cases} RCH_2COOH + HOOCR' \\ RCOOH + HOOCH_2R' \end{cases}$$

In a symmetrical cyclic ketone, cleavage at either carbon adjacent to the carbonyl group gives the same product.

α-Halogenation. — Acetic acid can be chlorinated in the presence of a trace of iodine, and yields in succession chloroacetic acid, di-, and trichloroacetic acid. In contrast with the photochemical chlorination of methane, the halogen substitution can be conducted in discrete

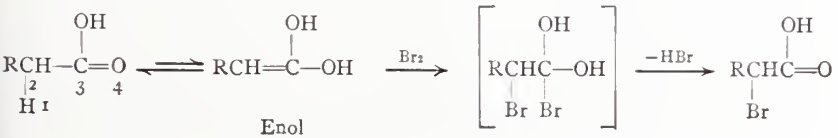
12.29

$$CH_3COOH \xrightarrow{Cl_2(I_2)} CH_2ClCOOH \xrightarrow{\text{Higher temp.}} CHCl_2COOH \xrightarrow{\text{Higher temp.}} CCl_3COOH$$

stages, and either the mono- or the dichloro compound can be prepared in good yield and in satisfactory purity by merely introducing chlorine slowly until the proper increase in weight is observed. Bromination of acids also can be effected readily, for example with use of phosphorus trichloride as catalyst:

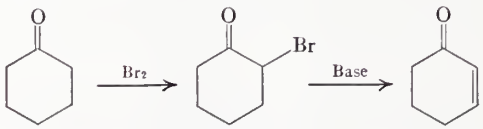
$$\underset{\substack{\alpha \\ \text{Caproic acid}}}{CH_3CH_2CH_2CH_2CH_2CO_2H} \xrightarrow[83\text{–}89\%]{Br_2(PCl_3),\ 65\text{–}70^\circ} \underset{\alpha\text{-Bromocaproic acid}}{CH_3CH_2CH_2CH_2CHBrCO_2H}$$

Bromine enters exclusively the activated α-position adjacent to the unsaturated carbonyl group, and activation by C=O can be understood as affording opportunity for production of an enol, through which



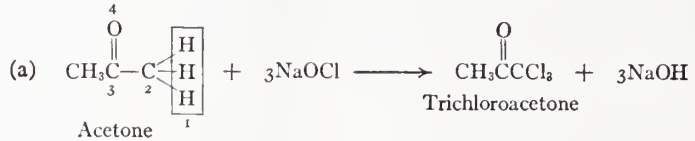
Mechanism of α-bromination

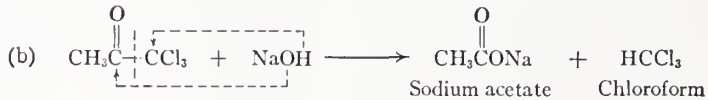
the α-bromo acid can be formed by a process of addition-elimination. An acid $RCH_2CH_2CO_2H$ yields first the α-bromo acid and then the α,α-dibromo acid, $RCH_2CBr_2CO_2H$; but, as expected, β- or other positions in the chain are not attacked. The acid $(CH_3)_3CCO_2H$ has no hydrogen on the α-carbon atom and it does not yield a halo-substitution product. Information regarding the structure of an unknown mono- or polycarboxylic acid can sometimes be gained by determination of the number of α-bromine atoms that can be introduced. Ketones can be similarly α-brominated. The sequence of bromination and elimination of hydrogen bromide is useful for production of α,β-unsaturated ketones.



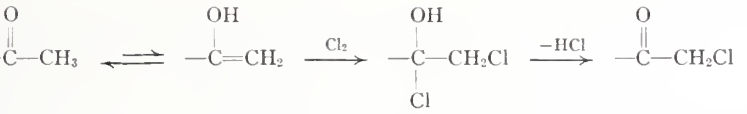
12.30 **Haloform Reaction.** — The trihalomethanes, chloroform (b.p. 61°), bromoform (b.p. 150°), and iodoform (m.p. 119°), are obtained easily by a process known as the haloform reaction (chloroform is so named because the structure is derivable from that of formic acid, HCOOH, by replacement of all oxygen substituents by chlorine atoms). This process consists in treatment of acetone with a solution of sodium hypochlorite. In the first phase of the reaction (a) one methyl group

α-Chlorination and alkali cleavage





is fully substituted by chlorine, and in the second (b) alkaline cleavage of the trichloroacetone occurs with production of sodium acetate and chloroform. Since sufficient alkali to bring about the cleavage is produced in the initial chlorination, the reactions proceed together and require a single operation. Both reactions have points in common with phenomena already discussed. The hydrogen atoms in acetone that suffer ready replacement are in a position (1) to be activated by the adjacent carbon–oxygen double bond (3,4). The ketone is in equilibrium with a trace of the enol (c), which adds chlorine to give a transient intermediate that loses hydrogen chloride and gives the substitution product. After the first halogen has entered the acetone

(c) 

molecule, a choice is open between further substitution in the same methyl group or in the one that is still intact, for both are equally activated by the carbonyl group. Since chlorine is a close neighbor of oxygen in the periodic table, analogy between the process of chlorination and that of oxidation is expected, and it has been noted (4.2) that an already oxidized site in a molecule is more susceptible to further oxidation than unoxidized sites. Thus chlorine is more prone to attack the already partly chlorinated carbon atom than the intact methyl group. The cleavage reaction (b) finds some analogy in the oxidative cleavage of *vic*-glycols (4.15), described as rupture of a weak bond connecting two oxidized carbon atoms. In the present instance the bond between the oxidized and the chlorinated carbon evidently is weak, or labile, and suffers easy rupture.

Chloroform is also obtainable in good yield by the action of hypochlorite on ethyl alcohol, for the reagent has oxidizing properties and acts initially by oxidizing the alcohol to acetaldehyde (d); the reac-

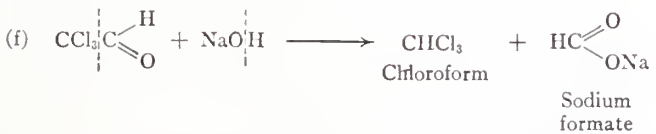
12.31

Chloroform from ethyl alcohol

(d) $CH_3CH_2OH + NaOCl \longrightarrow CH_3CHO + NaCl + H_2O$

tions of halogen substitution (e) and cleavage (f) then follow the same course as before:

(e) 

(f) 

Either acetone or alcohol can be employed satisfactorily for technical production of chloroform; at the end of the reaction the halide is removed by distillation from the alkaline solution of sodium acetate or formate. Sodium hypobromite and hypoiodite react in the same manner and yield bromoform ($CHBr_3$) and iodoform (CHI_3), respectively. The iodoform reaction is particularly well adapted to test purposes because this substance has properties that make it easily recognized and identified. Iodoform is a crystalline yellow solid, m.p. 119°, with a characteristic odor that reveals the presence of traces of the substance; it is sparingly soluble in water and a quantity of only a few milligrams separates in fine yellow crystals from an aqueous medium and can be identified by melting-point and mixed melting-point deter-

Iodoform test

minations. One application of the test is in distinguishing ethyl from methyl alcohol; ethyl alcohol gives a positive test, but methyl alcohol is converted into formaldehyde, which cannot yield iodoform, and hence the test is negative.

12.32 Acetaldehyde is the only aldehyde that gives the iodoform test, but all ketones that, like acetone, have at least one methyl group joined to the carbonyl group yield iodoform on reaction with iodine in sodium hydroxide solution. Thus all methyl ketones give a positive response in the test:

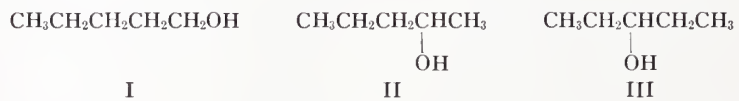
$$RCOCH_3 \xrightarrow{NaOI} RCOCI_3 \xrightarrow{NaOH} RCOONa + CHI_3$$

Secondary alcohols undergo oxidation by sodium hypoiodite to ketones, and those that yield methyl ketones likewise give a positive result:

$$RCHOHCH_3 \xrightarrow{NaOI} RCOCH_3 \xrightarrow{NaOI} CHI_3$$

Generalization

Thus the iodoform reaction is exhibited by acetaldehyde, by methyl ketones, and by such alcohols as can yield acetaldehyde or a methyl ketone on oxidation. The test has important uses in the diagnosis of structure. In the series of isomers pentanol-1 (I), pentanol-2 (II), and pentanol-3 (III), the first substance on oxidation with potassium dichromate gives an aldehyde, and the other two give ketones; the latter two compounds are distinguished by the fact that II yields iodoform on treatment with sodium hypoiodite and III gives a negative test.



I II III

SUMMARY

Addition Reactions

Bisulfite addition products:

$$RCHO \longrightarrow RCH(OH)SO_3Na.$$

Equilibrium displaced by excess $NaHSO_3$. Products are water-soluble, ether-insoluble solids. Aldehyde or ketone regenerated by treatment with HCl or NaOH. Additive power greatest for aldehydes and in ketones decreases with increasing size of the two alkyl groups due to steric hindrance. A cyclic ketone is less hindered than a related noncyclic ketone. A phenyl group, due to resonance, decreases double-bond character, and hence reactivity, of the carbonyl group. Esters, because of resonance, do not add bisulfite.

HCN-addition: nucleophilic attack by CN^- at positively polarized carbon. Cyanohydrin synthesis of the α-hydroxy acid mandelic acid,

$$C_6H_5CH(OH)CO_2H.$$

Use of the bisulfite addition compound + NaCN (in place of toxic HCN).

Grignard reaction:

$$>C{=}O + R^-Mg^+Br \longrightarrow >C(R)OMgBr \longrightarrow >C(R)OH.$$

Aldehyde $\longrightarrow$ *sec*-alcohol. Ketone $\longrightarrow$ *t*-alcohol of types $R_2R'COH$ or $RR'R''COH$. Ester (less reactive because of resonance) $\longrightarrow$ *t*-alcohol of types $RR'R'COH$ and R_3COH. Formaldehyde $\longrightarrow$ primary alcohol, RCH_2OH. Ethylene oxide

$\longrightarrow$ primary alcohol, RCH_2CH_2OH. Carbon dioxide $\longrightarrow$ RCOOH. Acid chloride (more reactive than an ester) $\longrightarrow$ ketone. Order of reactivity, $RCOF > RCOCl > RCOBr$, shows reaction to involve addition, not replacement.

Reduction, $>C{=}O \longrightarrow >CHOH$, with lithium aluminum hydride, $LiAlH_4$, in dry ether. The reagent adds like a Grignard reagent; 1 mole reduces 4 moles of ketone. Reduction of an ester: $RCOOCH_3 \longrightarrow RCH_2OH + HOCH_3$. Mechanism: addition, decomposition to an aldehyde, reduction of the aldehyde.

Bimolecular reduction of acetone with magnesium amalgam to pinacol (through a biradical). Aldehydes (more reactive) are reduced unimolecularly. Photochemical reduction of benzophenone by isopropyl alcohol (hydrogen donor) to benzopinacol.

Condensation with amines:

$$>C{=}O + H_2N{-} \longrightarrow >C{=}N{-}.$$

Hydroxylamine (H_2NOH) gives oximes, hydrazine (H_2NNH_2) gives hydrazones, phenylhydrazine ($C_6H_5N_2^+Cl^- + NaHSO_3$) gives phenylhydrazones. Qualitative test for aldehydes and ketones (esters do not react with $C_6H_5NHNH_2$). Mechanism: OH^- removes H from H_2NOH to give $\bar{H}NOH$, which attacks $>C{=}O$; intermediate addition product loses water to form the oxime.

Wolff-Kishner reduction: $>C{=}O + H_2NNH_2 \longrightarrow >C{=}NNH_2 \longrightarrow >CH_2 + N_2$. Use triethylene glycol as solvent, reflux to form the hydrazone, distil off water until temperature is 200°, reflux further.

Aldol condensation. Requires activated α-H, is usually base-catalyzed. Mechanism: OH^- abstracts H from CH_3CHO to form $\bar{C}H_2CHO$; this nucleophile attacks polarized C of a second molecule. Aldol easily dehydrated to crotonaldehyde (activated α-H adjacent to β-OH). Benzaldehyde, with no α-H, serves as acceptor for aldol condensation with an aliphatic aldehyde: $C_6H_5CHO + CH_3CHO \longrightarrow C_6H_5CH{=}CHCHO$ (cinnamaldehyde).

Keto–Enol Tautomerism

Ethyl acetoacetate (β-keto ester):

$$CH_3COCH_2CO_2C_2H_5\ (93\%) \rightleftharpoons CH_3C(OH){=}CHCO_2C_2H_5\ (7\%).$$

Interconversion by 2,4-hydrogen shifts. Isolation of keto and enol forms: equilibration with acid or base catalyst. Diethyl malonate less enolic, acetylacetone more enolic.

Ketones, stable to oxidation in acidic solution, are cleaved by permanganate in the presence of alkali, which promotes enolization. Cyclohexanol $\longrightarrow$ cyclohexanone $\longrightarrow$ adipic acid. Cyclopentanone $\longrightarrow$ glutaric acid.

α-Halogenation. Acetic acid + Cl_2 (I_2 as catalyst) $\longrightarrow CH_2ClCO_2H \longrightarrow CHCl_2CO_2H \longrightarrow CCl_3CO_2H$. Only α-H substituted. Mechanism: addition of halogen to double bond of enol, elimination of HX. Ketones similarly α-halogenated. A useful sequence: $-CH_2CH_2CO- \longrightarrow -CH_2CHBrCO- \longrightarrow -CH{=}CHCO-$.

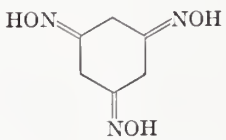
Haloform reaction: $RCOCH_3 \longrightarrow RCOCl_3 \longrightarrow RCOOH + HCCl_3$. Steps involved: replacement of the active H in one CH_3 by Cl (through the enol, the second and third chlorine atoms attack the already chlorinated carbon), alkaline cleavage of the bond connecting oxidized and chlorinated carbons. Practical preparation of chloroform from either acetone or ethanol. Value of the reaction as a route to acids.

Iodoform test. Properties of CHI_3 favorable for identification: odor, color, sparing solubility in water, solid substance (mixed m.p. determination). Compounds that give positive test: methyl ketones, ethanol, *sec*-alcohols that yield methyl ketones on oxidation.

PROBLEMS

1. Indicate Grignard syntheses of the following substances from *n*-propylmagnesium bromide and any second component desired:
   (*a*) 2-Methylpentanol-2
   (*b*) 4-Methylheptanol-4
   (*c*) *n*-Butyl alcohol
   (*d*) *n*-Amyl alcohol
   (*e*) Methylethyl-*n*-propylcarbinol
2. Ethylene oxide is related to formaldehyde in the same way that cyclopropane is related to ethylene: 3-membered ring vs. double bond. Cyclopropane resembles ethylene in ability to add Br_2, HBr (but is not attacked by $KMnO_4$); ethylene oxide resembles formaldehyde in reactivity to Grignard reagents. From this analogy, what conclusion can be drawn about the normal angle between the two oxygen valences in organic oxygen compounds?

3. Which would you expect to be the more reactive (e.g. in addition of $NaHSO_3$): benzaldehyde or hexahydrobenzaldehyde ($C_6H_{11}CHO$)?
4. Which of the following substances would be expected to give a positive iodoform test?
   (*a*) $CH_3CH_2CH_2CH(CH_3)CH_2OH$
   (*b*) $CH_3CH_2CH_2CHOHCH_3$
   (*c*) $CH_3CH(CH_3)CHOHCH_2CH_3$
   (*d*) CH_2OHCH_2OH
   (*e*) $CH_3COCH_2CH_2CH_2COOH$
   (*f*) CH_3COOH
   (*g*) $C_6H_5CHOHCH_3$
   (*h*) $(CH_3)_3COH$
5. A hydrocarbon C_7H_{12} yields cyclopentanecarboxylic acid on chromic acid oxidation. On reaction with concentrated sulfuric acid followed by hydrolysis it yields an alcohol, $C_7H_{14}O$, that gives a positive iodoform test. What is the structure of the hydrocarbon?
6. Suggest an ionic mechanism for the ester condensation of two molecules of ethyl acetate in the presence of sodium ethoxide to give ethyl acetoacetate (analogies: oxime-formation, aldol condensation).
7. Predict the structure of the product resulting from the reaction of ethylene oxide with hydrogen cyanide.
8. A substance $C_5H_{12}O$ yields an oxidation product $C_5H_{10}O$ that reacts with phenylhydrazine and gives a positive iodoform test. The original substance also can be dehydrated with sulfuric acid to a hydrocarbon C_5H_{10}, and this on oxidation yields acetone. What is the structure of the substance?
9. A substance $C_5H_8O_2$ forms a dioxime, gives a positive iodoform test and a positive silver mirror test, and can be converted into *n*-pentane. What is its structure?
10. A compound $C_7H_{14}O_2$ (I) reacts with acetic anhydride to give $C_7H_{13}O(OCOCH_3)$ (II); it does not react with phenylhydrazine. When treated with HIO_4, I gives $C_7H_{12}O_2$ (III), which with H_2NOH gives $C_7H_{12}(=NOH)_2$, reduces Fehling's solution, and on treatment with NaOI consumes 4 moles of the reagent to give iodoform and $HOOC(CH_2)_4COOH$. Give a brief interpretation of the significance of each of the observations recorded and deduce the structure of I.
11. What method of experimentation would distinguish between the following isomeric acids:
   (*a*) $CH_3CH_2CH(CH_3)CO_2H$
   (*b*) $(CH_3)_2CHCH_2CO_2H$
   (*c*) $(CH_3)_3CCO_2H$
12. The cyclic trioxime formulated gives, on hydrolysis, a nitrogen-free compound of the formula $C_6H_6O_3$ which does not react with phenylhydrazine but which forms a triacetate. What is its structure?



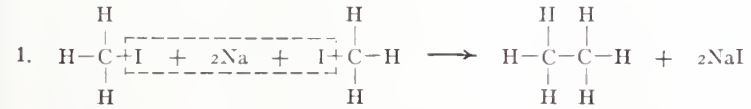
13. A physiologically active alkaloid A, isolated in 1885 by a Japanese investigator from the Chinese herb mahuang, became well known in the western world only in 1925, but has since been used widely in medicine, chiefly for treatment of bronchial asthma. The substance has the formula $C_{10}H_{15}ON$; it forms a hydrochloride from which the base is regenerated; it does not react with carbonyl reagents, and the iodoform test is also negative. Compound A reacts with acetic anhydride to give a neutral substance B, $C_{14}H_{19}O_3N$, and with nitrous acid to give a neutral yellow oil C, $C_{10}H_{14}O_2N_2$. Permanganate oxidation of A gives benzoic acid, and oxidation of A with periodic acid affords benzaldehyde, acetaldehyde, and methylamine (periodic acid cleaves *vic*-amino alcohols as well as *vic*-glycols). Deduce the structure of A and devise a method for its synthesis.

CHAPTER 13

SYNTHESIS

Hydrocarbons by Coupling. In 1855 the French chemist Adolphe Wurtz discovered that treatment of an alkyl halide with metallic sodium removes halogen from two molecules of the halide and effects coupling of the alkyl groups. Methyl iodide thus affords ethane (1). Actually, the reaction probably involves formation of methylsodium (2), which then interacts with methyl iodide (3). The second step is thus analogous to the Williamson ether synthesis (4). The

13.1

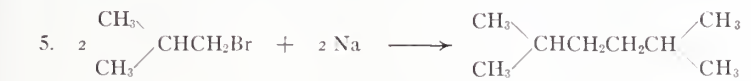


1. $H-C(H,H)-I + 2Na + I-C(H,H)-H \longrightarrow H-C(H,H)-C(H,H)-H + 2NaI$

Wurtz synthesis

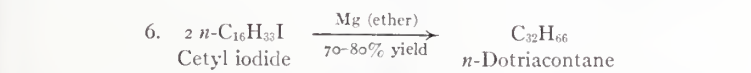
2. $CH_3I + 2\,Na \longrightarrow CH_3Na + NaI$
3. $CH_3Na + ICH_3 \longrightarrow CH_3CH_3 + NaI$
4. $CH_3ONa + ICH_3 \longrightarrow CH_3OCH_3 + NaI$

Wurtz synthesis provides a simple route to symmetrical hydrocarbons, for example, 2,5-dimethylhexane from isobutyl bromide (5). The



5. $2\,(CH_3)_2CHCH_2Br + 2\,Na \longrightarrow (CH_3)_2CHCH_2CH_2CH(CH_3)_2$

normal C_{32}-hydrocarbon can be synthesized starting with cetyl alcohol, a C_{16}-alcohol isolated from spermaceti wax. This is converted into the iodide, and two cetyl groups are coupled by reaction either with sodium amalgam in alcohol-ether or with magnesium (6).



6. $2\,n\text{-}C_{16}H_{33}I \xrightarrow[70\text{–}80\%\ \text{yield}]{Mg\ (ether)} C_{32}H_{66}$
   Cetyl iodide → *n*-Dotriacontane

A general expression for the Wurtz synthesis is:

13.2



$2\,RX + 2\,Na \longrightarrow RR + 2\,NaX$
Alkyl halide → Alkane

It might appear that the synthesis could be varied by use of two different alkyl halides, for example:

$$\underset{n\text{-Butyl iodide}}{CH_3CH_2CH_2CH_2I} + \underset{n\text{-Propyl iodide}}{ICH_2CH_2CH_3} \xrightarrow{2\ Na} \underset{n\text{-Heptane}}{CH_3CH_2CH_2CH_2CH_2CH_2CH_3}$$

Limitation

The reaction mixture, however, contains many millions of molecules of each halide, and although some butyl iodide molecules will react with molecules of propyl iodide and yield heptane as pictured, some will combine with each other and produce octane. The total result can be represented as follows:

$$CH_3CH_2CH_2CH_2I + CH_3CH_2CH_2I \xrightarrow{2\ Na} \begin{cases} n\text{-}C_6H_{14}, \text{ b.p. } 69° \\ n\text{-}C_7H_{16}, \text{ b.p. } 98° \\ n\text{-}C_8H_{18}, \text{ b.p. } 126° \end{cases}$$

RX + R′X ⟶ RR′, RR, R′R′

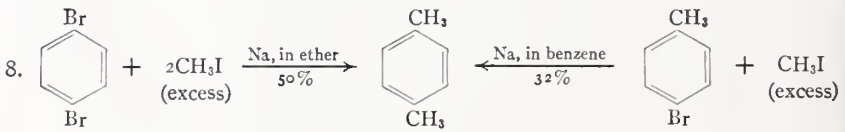
The reaction affords a mixture of three hydrocarbons that do not differ greatly in boiling point, and hence isolation of even a small amount of *n*-heptane in a moderately homogeneous condition would be difficult. It is therefore impracticable to utilize an unsymmetrical Wurtz reaction in synthesis.

13.3 Wurtz-Fittig synthesis

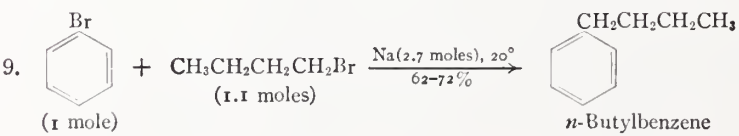
However, Rudolph Fittig showed in 1864 that unsymmetrical coupling is practical between an aryl halide and an alkyl halide (7).

$$7.\ ArX + RX + 2\,Na \longrightarrow ArR + 2\,NaX$$

Fittig's adaptation of the reaction to the preparation of compounds of mixed types can be applied successfully because the reaction products are easily separable. In the production of hydrocarbons of the type ArR, the by-products are the alkane RR and the aromatic hydrocarbon ArAr, and the difference in the boiling points is so profound that separation can be accomplished. For example, if methyl bromide is condensed with bromobenzene in the presence of two equivalents of sodium with the object of preparing toluene (b.p. 111°), the by-products are ethane and diphenyl (b.p. 254°). The reaction is illustrated (8) by the synthesis of *p*-xylene from either *p*-dibromobenzene or *p*-bromotoluene, and (9) by a particularly favorable synthesis of a mixed alkyl-aryl hydrocarbon requiring little excess alkyl halide.



Yields rather low



Wurtz was professor of chemistry at Strasbourg in southwestern France until the Franco-Prussian war, when the university temporarily changed to German hands. Fittig, a German, succeeded Baeyer to the Strasbourg chair in 1876. The discovery of the Friedel-Crafts method of alkylation of aromatic hydrocarbons in 1877 provided a useful alternative to the Wurtz-Fittig synthesis. 13.4

Strasbourg chemists

Another hydrocarbon synthesis involves coupling of a Grignard reagent with an allyl halide and is dependent upon the enhanced reactivity of this halide due to activation by the 3,4-double bond 13.5

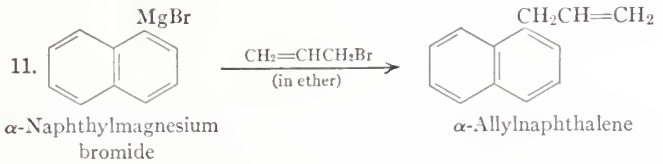
10. $CH_3CH_2CH_2CH_2MgBr + \overset{1}{Br}\overset{2}{C}H_2\overset{3}{C}H=\overset{4}{C}H_2 \xrightarrow{\text{(in ether)}}$

Allyl bromide

$CH_3CH_2CH_2CH_2CH_2CH=CH_2 + MgBr_2$

Heptene-1

Grignard coupling reaction



α-Naphthylmagnesium bromide

α-Allylnaphthalene

(11.8). The Grignard reagent can be either aliphatic (10) or aromatic (11), but the halide with which it is coupled must be of the allyl type to have the requisite reactivity.

Hydrocarbons via Synthetic Alcohols. — Since the Grignard reaction provides a versatile route to alcohols of all types, a hydrocarbon is often most readily obtained by the synthesis of an alcohol capable of being transformed into the hydrocarbon. 13.6

n-Heptane can be made by Grignard reaction of *n*-butylmagnesium bromide with propionaldehyde (hydrolysis of ROMgBr omitted from formulation), dehydration of the resulting alcohol, and catalytic hydrogenation. The dehydration step would be expected to proceed 13.7

$$CH_3CH_2CH_2CH_2MgBr \xrightarrow{O=CHCH_2CH_3} CH_3CH_2CH_2\overset{4}{C}H_2\overset{3}{C}H(OH)\overset{2}{C}H_2CH_3 \xrightarrow{-H_2O}$$

$$\left\{\begin{matrix} CH_3CH_2CH_2CH=CHCH_2CH_3 \\ CH_3CH_2CH_2CH_2CH=CHCH_3 \end{matrix}\right\} \xrightarrow{H_2\ (Pt)} CH_3CH_2CH_2CH_2CH_2CH_2CH_3$$

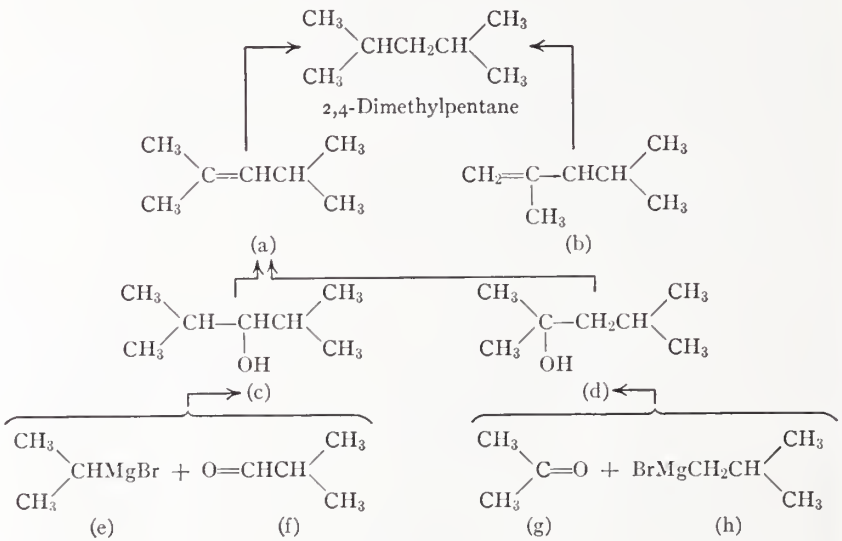
Example 1

by elimination of hydrogen from C_2 and from C_4 to about the same extent, since each carbon carries two hydrogen atoms, but it is immaterial that dehydration gives a mixture of two alkenes for they both yield *n*-heptane on hydrogenation.

Suppose that 2,4-dimethylpentane is required and the starting materials available are methyl and ethyl alcohol, the two propyl alcohols, and the four butyl alcohols. Any of these can be converted through the halides to the Grignard reagents; the primary alcohols 13.8

Example 2

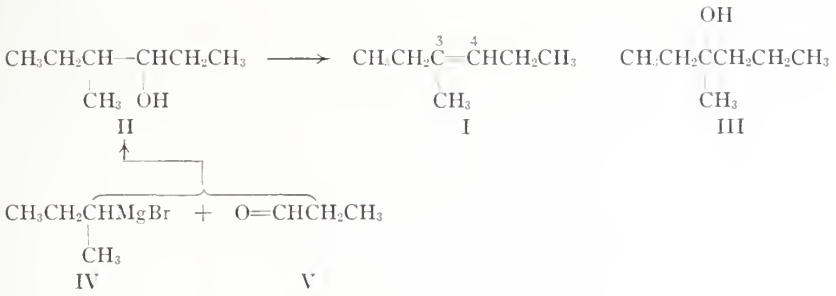
can be oxidized to either the aldehydes or the acids and the acids can be esterified; the secondary alcohols are potential sources of the corresponding ketones. 2,4-Dimethylpentane would result from hy-



drogenation of either alkene (a) or alkene (b). Alkene (a) could be obtained by dehydration of either alcohol (c) or alcohol (d), and consideration of the Saytzeff rule (10.8) shows that (a) should be the sole product of both dehydrations. Both alcohols are available by Grignard syntheses from components obtainable from isopropyl and isobutyl alcohol, and hence two complete routes are at hand from available starting materials through alkene (a) to the desired alkane. Alkene (b) does not afford a satisfactory alternative path because there is no simple method of preparation. Dehydration of alcohol (d), with the hydroxyl group at C_2, gives (a) not (b), and the isomeric alcohol with the hydroxyl at C_1 could not be constructed by a Grignard reaction of C_1–C_4 components. Note that the problem was solved by working back in steps from the desired product to available starting materials. This approach is usually better than to center attention on starting materials.

13.9 ——— ***Example 3***

The problem is to synthesize 3-methylhexene-3 (I) from alcohols having not more than four carbon atoms. Two possible precursors come to mind, one with the hydroxyl at the 3-position (III) and the other with this group at position 4 (II). Structure III is disadvantageous because the hydroxylated carbon atom is flanked on each side by a methylene group (—CH_2—) and dehydration would probably occur to about the same extent in each of the two possible directions. In the alcohol II, however, one carbon adjacent to the hydroxylated

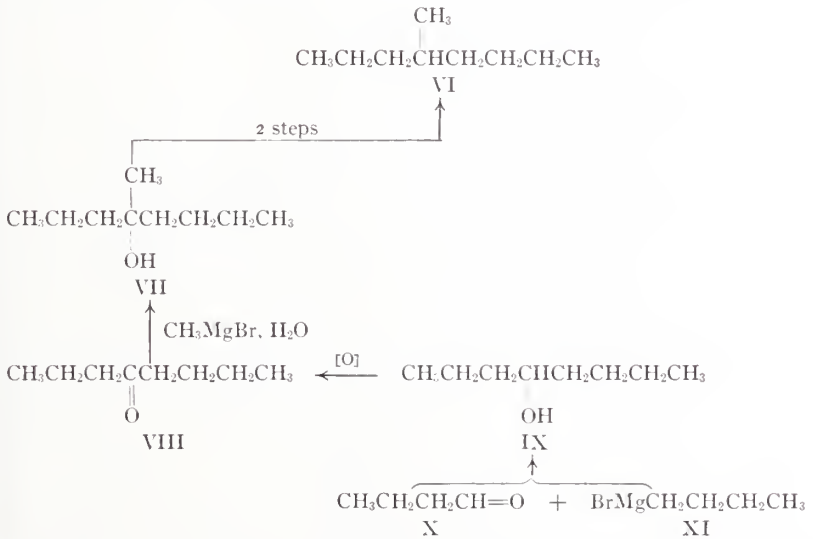


carbon carries a lone hydrogen atom whereas the alternate position carries two, and hence, in analogy with known cases, dehydration can be expected to yield the desired alkene I. Synthesis of the intermediate alcohol II can be accomplished by interaction of *sec*-butylmagnesium bromide (IV) with propionaldehyde (V), and these substances in turn are obtainable from *sec*-butyl alcohol and *n*-propyl alcohol, respectively.

The synthesis of 4-methyloctane (VI) from C_1- to C_4-alcohols obviously calls for a process more elaborate than the union of two parts, for the hydrocarbon contains nine carbon atoms. It could be obtained from the alcohol VII either by dehydration and catalytic hydrogena-

13.10

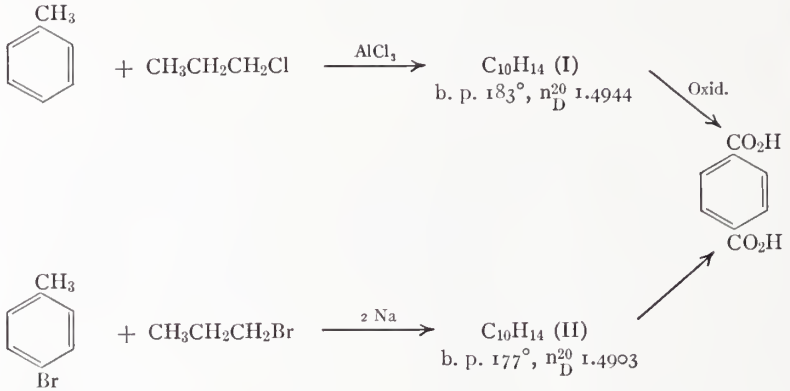
Example 4



tion or by conversion into the bromide, preparation of the Grignard reagent, and treatment with water. The alcohol VII could be synthesized, in turn, by addition of methyl Grignard reagent to the ketone VIII, and this substance would result from oxidation of the secondary alcohol IX, obtainable by interaction of *n*-butyraldehyde (X) with *n*-butylmagnesium bromide (XI).

13.11 From what has been stated thus far about the reactions involved, one would expect to obtain the same product by Friedel-Crafts reaction of toluene with *n*-propyl chloride and by Wurtz-Fittig reaction of *p*-bromotoluene with *n*-propyl bromide. However, the two reactions yield different products, I and II. These are isomeric hydrocarbons

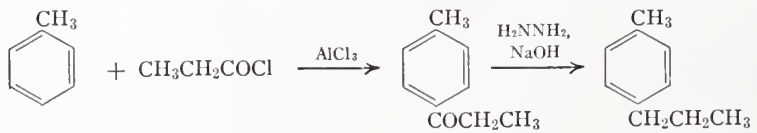
Example 5

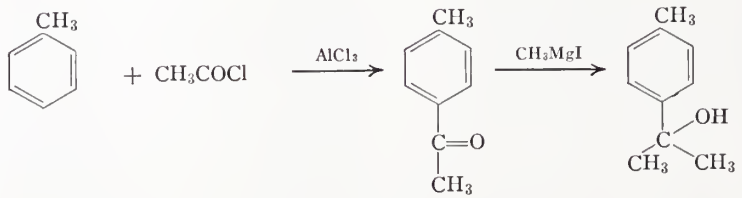


differing in both boiling point and refractive index (n_D^{20}). They both have the composition of the expected *p*-methyl-*n*-propylbenzene, and both on oxidation yield terephthalic acid; hence one must be *p*-methyl-*n*-propylbenzene and the other *p*-methyl-*i*-propylbenzene, resulting from a rearrangement of the *n*-propyl group in one reaction or the other.

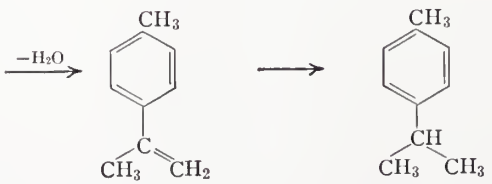
One reaction is abnormal

13.12 To determine which reaction gives the normal product and which the abnormal one, it is necessary to synthesize the two hydrocarbons





Unambiguous syntheses



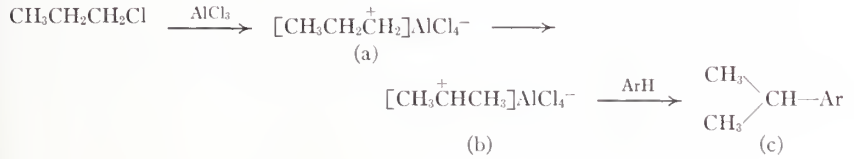
p-Cymene
I

by reactions that establish the structures unambiguously. The Friedel-Crafts ketone synthesis from an acid chloride and an aromatic hydrocarbon is such a reaction. Acylation of toluene with propionyl chloride and Wolff-Kishner reduction (12.21) gives a product identical with that of the Wurtz-Fittig reaction (II), and hence this reaction proceeds normally. A synthesis of the isomer involves Friedel-Crafts reaction to introduce a *p*-aceto group, addition of methyl Grignard reagent to the carbonyl group, dehydration, and saturation of the double bond by hydrogenation; the last step can be done so easily that there is no danger of saturation of the much less reactive phenyl group. The product, which occurs in various natural oils and which is known as *p*-cymene, is identical with the hydrocarbon I resulting from Friedel-Crafts alkylation with *n*-propyl chloride, and this reaction is thus recognized as proceeding with rearrangement of the alkyl group.

Friedel-Crafts alkylation abnormal

An interpretation of the rearrangement can be inferred from the mechanism of the Friedel-Crafts reaction (6.9). The first step is formation of an ionic complex of halide with catalyst (a). The cation

13.13



Interpretation of rearrangement

of the complex (a) is less stable than that of (b), since the latter has two electron-releasing groups to balance the charge and not just one, and hence (a) rearranges to (b) and the reaction product (c) contains the isopropyl group.

The problem is to devise syntheses, utilizing Grignard reactions, of all possible mono-, di-, tri-, and tetraphenyl derivatives of ethylene starting with compounds available from benzene or toluene, and any aliphatic reagents required. Disregard stereoisomerism of

13.14

Example 6

$$C_6H_5CH{=}CHC_6H_5.$$

Halides available for conversion into Grignard reagents include bromobenzene, from benzene by bromination, and benzyl chloride, $C_6H_5CH_2Cl$, by chlorination of toluene in the sunlight (11.18). One carbonyl component required is benzaldehyde, available from toluene via benzal chloride ($C_6H_5CHCl_2$, 11.18). Another is benzophenone, $(C_6H_5)_2C{=}O$. This can be made by oxidation of toluene to benzoic acid, reaction of this acid with thionyl chloride to form benzoyl chloride (C_6H_5COCl), and Friedel-Crafts condensation with benzene.

13.15

Try the problem before reading further

Reduction of benzophenone to the alcohol $(C_6H_5)_2CHOH$ and reaction of this with hydrobromic acid gives the further halide $(C_6H_5)_2CHBr$.

13.16 From these and accessory aliphatic reagents, the five hydrocarbons can be synthesized by the reactions formulated.

(a) $C_6H_5MgBr + O{=}CHCH_3 \longrightarrow C_6H_5CHCH_3 \xrightarrow{-H_2O} C_6H_5CH{=}CH_2$ (Styrene)
OH

(b) $(C_6H_5)_2C{=}O + BrMgCH_3 \longrightarrow (C_6H_5)_2C{-}CH_3 \xrightarrow{-H_2O} (C_6H_5)_2C{=}CH_2$
OH

(c) $C_6H_5CH{=}O + ClMgCH_2C_6H_5 \longrightarrow C_6H_5CH{-}CH_2C_6H_5 \xrightarrow{-H_2O} C_6H_5CH{=}CHC_6H_5$
OH

(d) $(C_6H_5)_2C{=}O + ClMgCH_2C_6H_5 \longrightarrow (C_6H_5)_2C{-}CH_2C_6H_5 \xrightarrow{-H_2O} (C_6H_5)_2C{=}CHC_6H_5$
OH

(e) $(C_6H_5)_2C{=}O + BrMgCH(C_6H_5)_2 \longrightarrow (C_6H_5)_2C{-}CH(C_6H_5)_2 \xrightarrow{-H_2O} (C_6H_5)_2C{=}C(C_6H_5)_2$
OH

13.17 **Malonic Ester Synthesis.** — A crystalline acid occurring in various fruit juices was named malic acid from the Latin word *malum* meaning apple, since the apple was the fruit from which the acid was first isolated. When malic acid was later found to yield a new acid

Discovery and naming of the acid

$$\underset{\substack{\text{HOCHCOOH}\\ \text{CH}_2\text{COOH}\\ \text{Malic acid}}}{} \xrightarrow{[O]} \underset{\substack{\text{COOH}\\ \text{CH}_2\text{COOH}\\ \text{Malonic acid}}}{} + CO_2 + H_2O$$

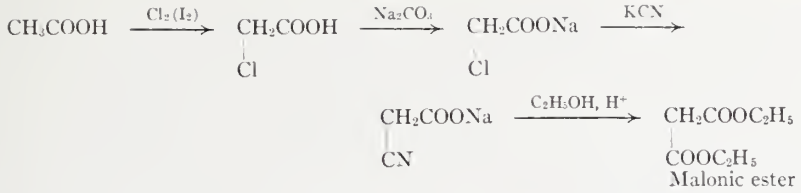
on oxidation, the new substance was given the name malonic acid: malic plus the letter o for oxidation (and the letter n for euphony). Malonic acid is unique in having two carboxyl groups on the same carbon atom. It is not so unstable as a *gem*-diol, $R_2C(OH)_2$, which spontaneously loses water, but differs from ordinary acids and from the other diacids in losing carbon dioxide when heated at about 100° to afford acetic acid in high yield. Substituted malonic acids of the

Ready decarboxylation

$$\underset{\substack{\text{COOH}\\ \text{CH}_2\text{COOH}}}{} \xrightarrow{\text{Heat}} CH_3COOH + CO_2$$

types $RCH(COOH)_2$ likewise undergo smooth decarboxylation and are available by a method to be described.

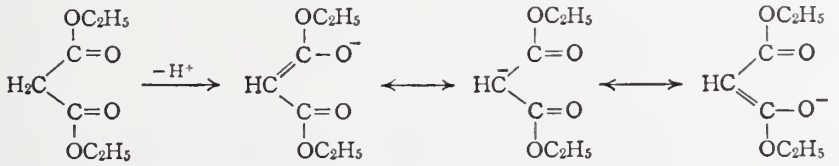
13.18 Diethyl malonate, commonly called malonic ester, is made by α-chlorination of acetic acid, neutralization, replacement of chlorine by a nitrile group, and reaction with ethanol and a mineral acid. The



Malonic ester

Preparation of the ester

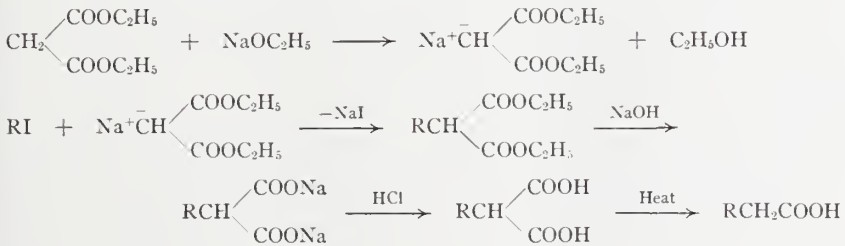
two carboxylate groups of malonic ester activate the central hydrogen atoms and, although an enol form is present in only trace amounts, the ester reacts with sodium ethoxide to form a sodium enolate, the anion of which is stabilized by resonance. Although the charge is



Resonance stabilization of enolate anion

distributed between carbon and oxygen atoms, the sodium enolate is appropriately written as $Na^+C^-H(COOC_2H_5)_2$ because the product of reaction of the substance with RX is the C-alkyl derivative $RCH(COOC_2H_5)_2$. Hydrolysis of the alkylation product gives the substituted malonic acid $RCH(COOH)_2$, and this on gentle heating loses carbon dioxide to form the acid RCH_2COOH. The steps in the malonic ester synthesis are thus as follows:

Alkylation



Steps in the synthesis

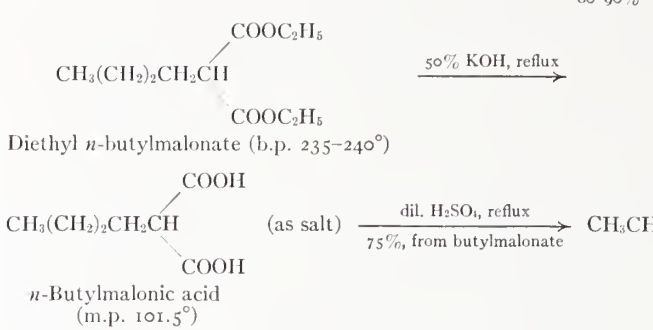
The overall process accomplishes replacement of the halogen atom of the alkyl halide by the acetic acid residue. An example is the

13.19

Synthesis of RCH_2CO_2H



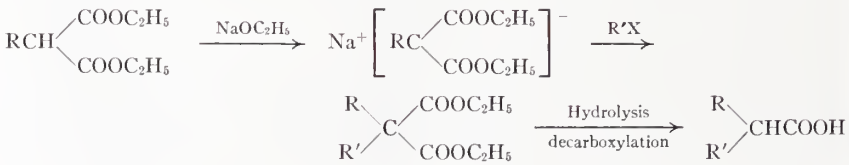
synthesis of caproic acid starting with *n*-butyl bromide. Metallic sodium is dissolved in ethanol to give a solution of sodium ethoxide, and malonic ester is slowly introduced, followed by an equivalent amount of *n*-butyl bromide. The substituted malonic ester is separated by removing the bulk of the alcohol and adding water, and it is hydrolyzed with boiling potassium hydroxide solution. The resulting *n*-butylmalonic acid can be isolated as a solid and the decarboxylation conducted by heating the molten material at 150°. A simpler method is to render the aqueous solution strongly acidic with sulfuric acid and



reflux the mixture; the mineral acid catalyzes loss of carbon dioxide at a temperature not much above 100°.

13.20 A monosubstituted malonic ester still has a hydrogen atom replaceable by sodium and therefore available for a second alkylation. The general method thus can be extended to the synthesis of dialkylacetic acids:

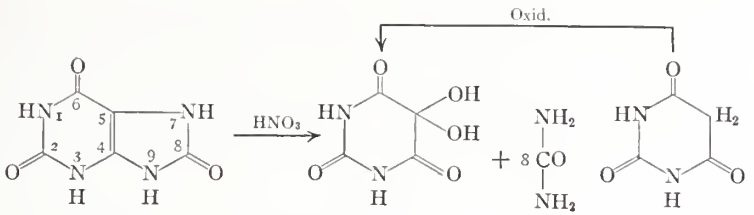
Synthesis of $\begin{matrix} R \\ R' \end{matrix}\!\!>\!CHCO_2H$



13.21 **Barbiturates.** — Malonic ester features in an entirely different kind of synthesis, the history of which goes back to the discovery of uric acid by Carl Wilhelm Scheele in Sweden in 1776. Uric acid is the chief end product of metabolism of proteins in snakes and birds. It occurs normally in human urine, but in only very small amounts. Patients suffering from gout excrete excessive amounts of uric acid, and light brown pebbles of the sparingly soluble solid sometimes lodge in the bladder or kidney and have to be removed by surgery. Early workers established the formula $C_5H_4O_3N_4$ and identified one product of pyrolytic decomposition as urea (H_2NCONH_2), the chief product of nitrogenous metabolism excreted in human urine. Extensive investigations by Baeyer in 1863–64 at what is now the Technical Institute of Berlin and by Emil Fischer at Berlin University in 1881–99 established the nature of a host of degradation products and eventually elucidated the structure of the natural product. Uric acid contains a six-membered heterocyclic ring fused to a five-membered heterocyclic ring; the former includes a ureide grouping at the 1,2,3-position and the latter a similar grouping at the 7,8,9-position. The acidity is due to the hydrogen at N_1, which is activated by the flanking carbonyl groups at C_2 and C_6; this part of the molecule is analogous to the acidic part of succinimide (9.24).

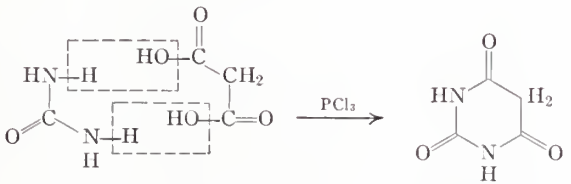
Discovery of uric acid

Structure elucidation by Baeyer and by E. Fischer



One of the degradations by which the structure of uric acid was unraveled involves oxidation with nitric acid to alloxan and urea. Alloxan is a stable hydrate of a 1,2,3-triketone, the central carbonyl group of which has unusual additive power because of the inductive effect of the two flanking electron-attracting groups. Baeyer, in a series of steps, discovered the further degradation product barbituric acid and named it for a friend, Barbara, and Fischer established the relationship between barbituric acid and alloxan by oxidation of the former to the latter. The structure of barbituric acid inferred from identification of the products of its hydrolysis was confirmed by synthesis from urea and malonic acid. The yield in the condensation

13.22

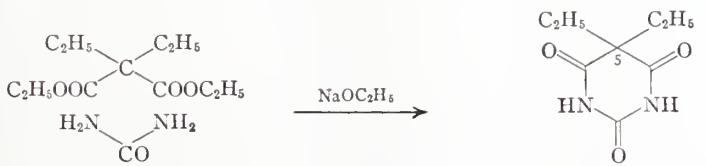


Synthesis of a cyclic ureide

is low because of the sensitivity of malonic acid to decarboxylation. Fischer later found that the procedure is greatly improved by use of malonic ester in place of the acid and of sodium ethoxide as the condensing agent.

In 1903 E. Fischer and J. von Mering applied this procedure to the synthesis of a number of derivatives of barbituric acid, some of which were found valuable as soporifics. 5,5-Diethylbarbituric acid has

13.23

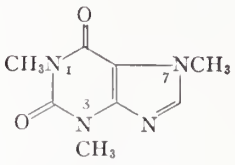


A sleep-inducing barbiturate

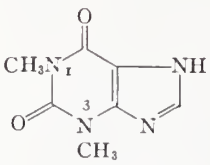
been widely used under the name veronal or barbital to induce sleep and to some extent as a sedative and in anesthesia.

13.24 It is curious that the alkaloids caffeine, theophylline, and theobromine bear a certain structural analogy to the barbiturates but have physiological activity of directly opposite type: they are stimulants. The coffee bean contains caffeine (1.5%); tea leaves contain caffeine

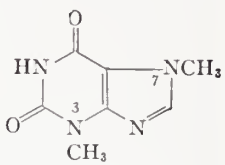
Stimulants



Caffeine



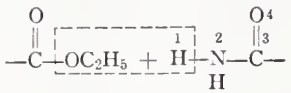
Theophylline



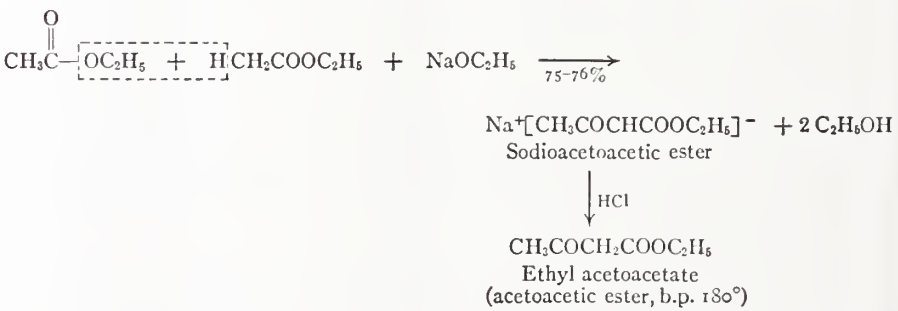
Theobromine

(5%) and theophylline (trace); cocoa beans (*Theobroma cacao*) contain theobromine (1.8%).

13.25 **Ester Condensation.** — The condensation of malonic ester with urea under the influence of sodium ethoxide involves elimination of ethanol between an ester group and a hydrogen activated by an adjacent carbonyl group:



A closely analogous reaction, called ester condensation, is illustrated by the condensation of two moles of ethyl acetate in the presence of



sodium ethoxide to form the sodium enolate of ethyl acetoacetate. Ethanol is eliminated between the ester group of one molecule and the activated α-hydrogen of another. The reaction is reversible, but a high yield can be obtained by distillation of the alcohol formed with displacement of the equilibrium. Acidification liberates free ethyl acetoacetate. This ester on standing with aqueous alkali at room temperature undergoes hydrolysis, and if the solution is neutralized carefully acetoacetic acid is liberated. If excess hydrochloric acid is

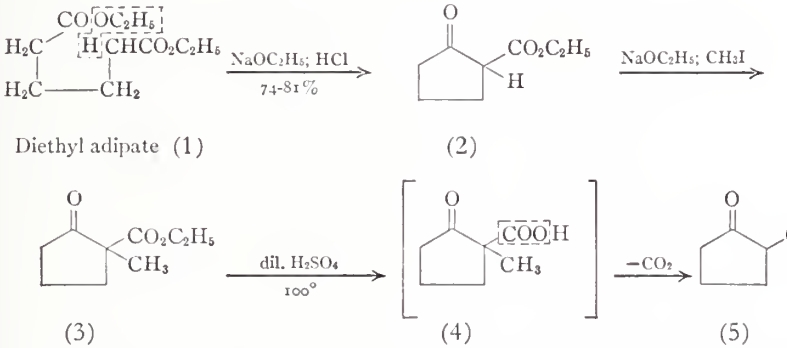


added and the solution warmed, carbon dioxide is evolved and acetone is formed. The behavior is characteristic of β-keto acids and analogous to the ready decarboxylation of malonic acids. A β-keto acid has a carboxyl and a keto group on the same carbon atom; a malonic acid has two similarly situated carboxyl groups.

Decarboxylation of a β-keto acid

Application of the ester condensation to effect intramolecular cyclization of a diester was first demonstrated by Walter Dieckmann and is called a Dieckmann condensation. For example, adipic acid,

13.26

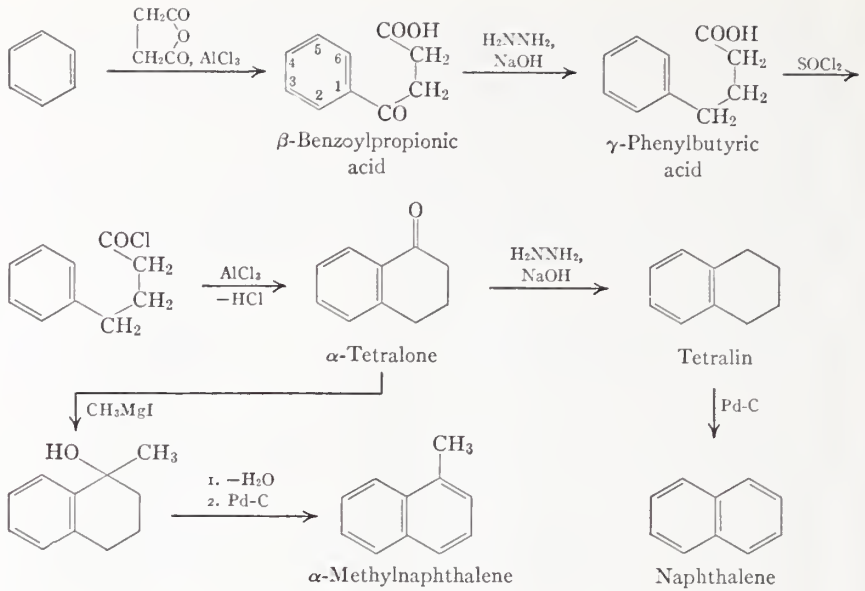


Dieckmann condensation

prepared by oxidation of cyclohexanone (12.28), is esterified and the ester (1) treated with sodium ethoxide. Elimination of ethanol closes the ring to give, after acidification, 2-carbethoxycyclopentanone (2). This β-keto ester is analogous to malonic ester and can be alkylated by treatment of the sodium enolate with methyl iodide to give (3). The product is likewise a β-keto ester, and on acid hydrolysis the β-keto acid initially formed loses carbon dioxide to give 2-methylcyclopentanone (5).

Succinic Anhydride Synthesis. — A useful method of building one aromatic ring onto another starts with a Friedel-Crafts reaction of an aromatic hydrocarbon with succinic anhydride. Benzene itself gives β-benzoylpropionic acid, and this is reducible by the Wolff-Kishner method (12.21) to γ-phenylbutyric acid. Reaction of the acid with thionyl chloride gives an acid chloride capable of undergoing intramolecular Friedel-Crafts cyclization to α-tetralone. Note that the acid chloride of β-benzoylpropionic acid does not undergo similar cyclization because the benzene ring to be substituted carries a deactivating carbonyl group which inhibits Friedel-Crafts acylation. α-Tetralone on Wolff-Kishner reduction affords tetralin, and this hydrocarbon can be dehydrogenated catalytically by heating it with palladium catalyst adsorbed on charcoal, best in a stream of carbon dioxide to entrain the hydrogen eliminated. This reversal of catalytic hydrogenation is possible because of the driving force of formation of a resonant aromatic ring. The last step completes a synthesis of

13.27



Naphthalene and α-methylnaphthalene from benzene

naphthalene from benzene, utilizing reactions that all proceed in high yield.

13.28 ***Variations in the synthesis***

The intermediate α-tetralone can be used for the synthesis of α-methylnaphthalene by a Grignard reaction, dehydration, and catalytic dehydrogenation of the methyldihydronaphthalene. The synthesis can be varied also by using a benzene derivative in place of benzene. Thus *p*-xylene put through the synthesis leading to naphthalene would yield 1,4-dimethylnaphthalene, and by the second synthesis would yield 1,4,5-trimethylnaphthalene. Toluene on succinoylation yields β-(4-methylbenzoyl)-propionic acid, and application of the first set of reactions formulated would give β-methylnaphthalene.

SUMMARY

Hydrocarbons by coupling. Wurtz reaction: $2\ RX + 2\ Na \longrightarrow RR$. Mechanism: $RX \longrightarrow RNa$; $RNa + XR \longrightarrow RR$ (cf. Williamson synthesis). Unsatisfactory for any but symmetrical hydrocarbons, since $RX + R'X$ (2 Na) $\longrightarrow RR'$, RR, and $R'R'$.

Wurtz-Fittig reaction: $ArX + 2\ Na + RX \longrightarrow ArR$ (separable from ArAr and RR because the three are of different types and b.p.).

Grignard coupling: $R(Ar)MgBr + BrCH_2CH{=}CH_2 \longrightarrow R(Ar)CH_2CH{=}CH_2$. Specific for highly reactive allyl halides.

Grignard synthesis of alcohols for conversion to alkenes and alkanes. The examples cited are listed below in the form of problems.

1. How synthesize *n*-heptane starting with a Grignard reaction of $RMgBr + RCHO$?

2. How can 2,4-dimethylpentane be synthesized from the starting materials: methyl, ethyl, the two propyl, and the four butyl alcohols? These can be converted to aldehydes, acids, esters, ketones, alkyl halides, and alkylmagnesium halides. Work the problem backwards: what alkenes would give the alkane on hydrogenation; what alcohols would serve as precursors for the alkenes; how can the alcohols be synthesized?

3. Devise a synthesis of 3-methylhexene-3 from alcohols having not more than four carbon atoms.

4. How can 4-methyloctane be synthesized from C_1- to C_4-alcohols?

5. The following problem is a variant of that cited in the text. Isobutyl bromide reacts with toluene in the presence of aluminum chloride to give a hydrocarbon A, and it reacts with *p*-bromotoluene and sodium to give an isomeric hydrocarbon B. What are the possible structures, and how could you prove which is which (suggestion: an alkyl side chain that has no hydrogen atoms on the carbon adjacent to the benzene ring is stable to oxidation)? How could you synthesize either A or B by a method that would prove its structure?

6. The problem is to synthesize all possible mono-, di-, tri-, and tetraphenyl derivatives of ethylene, using starting materials available from benzene and toluene, and any aliphatic reagents desired.

Malonic ester synthesis. Malic acid (from the apple), or α-hydroxysuccinic acid, on oxidation yields an acid named malonic: $HO_2CCH_2CO_2H$. Characteristic property: ready decarboxylation to $CH_3CO_2H + CO_2$. The diethyl ester, called malonic ester, prepared from CH_2ClCO_2H through the nitrile. In $CH_2(CO_2C_2H_5)_2$, activation of the methylene hydrogens by two carboxylate groups promotes reaction with $NaOC_2H_5$ to form the sodium enolate (resonance stabilized anion) represented as $Na^+\bar{C}H(CO_2C_2H_5)_2$. This on alkylation with RI gives $RCH(CO_2C_2H_5)_2$, which on hydrolysis and decarboxylation gives RCH_2CO_2H. Thus $RX \longrightarrow RCH_2CO_2H$. Synthesis of R_2CHCO_2H and of $RR'CHCO_2H$ also possible.

Barbiturates. Uric acid (urine, excretion of snakes and birds) has a six-membered ring fused to a five-membered ring and each ring contains a ureide group. Barbituric acid, a degradation product, was first synthesized by condensation of urea with malonic acid. E. Fischer improved the process by using malonic ester in place of the acid and discovered a useful soporific, diethylbarbituric acid. Key reaction:

$$—CO—OC_2H_5 + H—NHCO— \longrightarrow —CO—NHCO— \text{ (presence of } NaOC_2H_5).$$

Ester condensation involves the related reaction to form

$$CH_3CO—OC_2H_5 + H—CH_2CO_2C_2H_5 \longrightarrow CH_3CO—CH_2CO_2C_2H_5$$

ethyl acetoacetate (presence of $NaOC_2H_5$). Hydrolysis with cold alkali gives acetoacetic acid, $CH_3COCH_2CO_2H$; like other β-keto acids (and like the related malonic acid), this readily loses CO_2 to form acetone.

Dieckmann condensation: ester condensation of a diester to produce a cyclic β-keto ester. Diethyl adipate $\longrightarrow$ 2-carbethoxycyclopentanone. This ester on hydrolysis and decarboxylation yields cyclopentanone; it can also be methylated and converted into 2-methylcyclopentanone.

Succinic anhydride synthesis. Synthesis of naphthalene: benzene + succinic anhydride ($+AlCl_3$) $\longrightarrow$ β-benzoylpropionic acid; reduction of the keto group to give γ-phenylbutyric acid; conversion to the acid chloride and intramolecular Friedel-Crafts reaction to give α-tetralone; reduction to tetralin; palladium–charcoal dehydrogenation to naphthalene. Variations: use α-tetralone for the synthesis of α-methylnaphthalene; use toluene or *p*-xylene in place of benzene.

PROBLEMS

1. Devise syntheses of the following compounds, starting with any alcohols having not more than three carbon atoms and any desired components readily obtainable from these alcohols (the list of available starting materials thus includes C_3-compounds of the types RX, RMgX, RCHO, RCOR, RCO_2H; also ethylene oxide, allyl alcohol):
   (*a*) $(CH_3)_2CHCH_2OH$
   (*b*) $(CH_3)_2C(OH)CH_2CH_3$
   (*c*) $(CH_3CH_2)_3COH$
   (*d*) $CH_3CH_2CH_2CH_2CH_2OH$
   (*e*) 2-Methylbutene-2
   (*f*) 4-Methylpentene-1
   (*g*) 2,3-Dimethylbutene-2
   (*h*) Isobutane
   (*i*) 2-Methylpentane
   (*j*) 2,3,4-Trimethylpentane
2. Give syntheses of the following compounds from the starting materials of (1):
   (*a*) 4-Ethylheptane
   (*b*) 4-Methylpentadiene-1,3
   (*c*) Neopentyl alcohol, $(CH_3)_3CCH_2OH$
3. Devise syntheses of the following compounds starting with alcohols and derived substances having no more than four carbons:
   (*a*) 2,4-Dimethylpentene-2
   (*b*) 3-Methylhexanol-3
   (*c*) 2-Methylhexane
   (*d*) 2,2-Dimethylpentane
4. Plan a synthesis of octadiene-2,6 from cyclohexene.

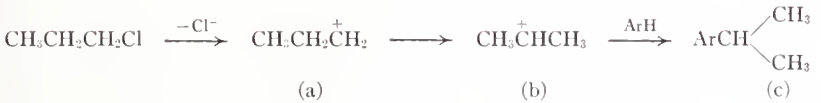
5. Starting with $C_6H_5CH_2Cl$, C_6H_5COCl, C_6H_5Br, and any aliphatic reagents desired, devise syntheses of:
   (*a*) $C_6H_5CH_2CO_2H$
   (*b*) $C_6H_5CH_2CH_2CO_2H$
   (*c*) $C_6H_5CH_2CH_2CH_2CO_2H$
   (*d*) $C_6H_5COC_6H_5$
6. What products would you expect to result from the action of $NaOC_2H_5$ on:
   (*a*) $C_6H_5COOC_2H_5 + CH_3COC_2H_5$
   (*b*) $CH_3OOCCH_2CH_2CH_2CH_2CH_2COOCH_3$
   (*c*) Urea and diethyl oxalate, $C_2H_5OOCCOOC_2H_5$
7. What would you expect to be the outcome of attempts to apply the succinic anhydride synthesis (13.27) to:
   (*a*) Thiophene
   (*b*) Pyridine
   (*c*) *m*-Xylene
8. From the following description of a synthesis, deduce the structure of the product. Friedel-Crafts reaction of phthalic anhydride with benzene; Wolff-Kishner reduction; reaction with $SOCl_2$; treatment of the product with $AlCl_3$; oxidation.

CHAPTER 14

REARRANGEMENTS

14.1 The example cited in the preceding chapter of a Friedel-Crafts alkylation in which *n*-propyl chloride reacts to give an isopropyl derivative of the aromatic hydrocarbon alkylated (13.13) illustrates a type of rearrangement not infrequently encountered. The rearrangement cited was interpreted as due to the fact that the carbonium ion (b) has greater stability than the initially formed ion (a), and hence that the product is an isopropyl derivative (c), rather than an

Rearrangement in Friedel-Crafts alkylation

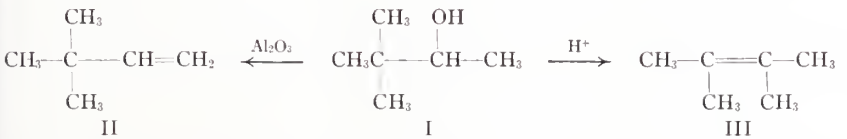


(a) (b) (c)

n-propyl derivative. Similar interpretations apply to a number of other rearrangements, some of which are described below.

14.2 **Wagner-Meerwein Rearrangement.** — Barring rearrangement, methyl-*t*-butylcarbinol (I) can eliminate the elements of water in only one way, namely, to form *t*-butylethylene (II). This normal, expected product is indeed what is obtained by catalytic dehydration of the alcohol over alumina. On the other hand, dehydration of I with a mineral acid gives the obviously rearranged product tetra-

Normal and abnormal dehydration



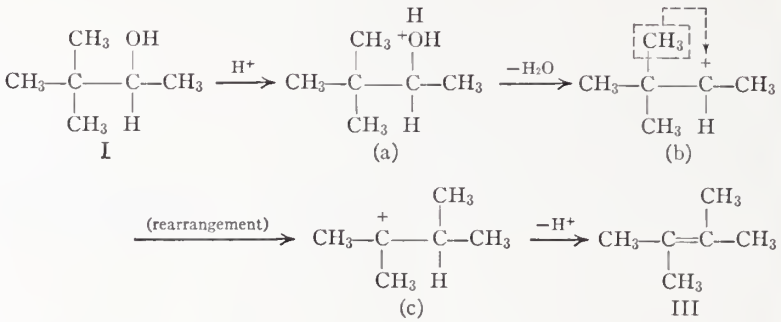
II I III

methylethylene (III). The occurrence of abnormal dehydration reactions of this type was recognized at about the same time (1899) by Gustav Wagner in Russia and by Hans Meerwein in Germany.

14.3 The rearrangement cited is interpreted as follows. The oxygen atom of the alcohol, functioning as a Lewis base, accepts a hydrogen ion to form the oxonium ion (a), which loses water to give the car-

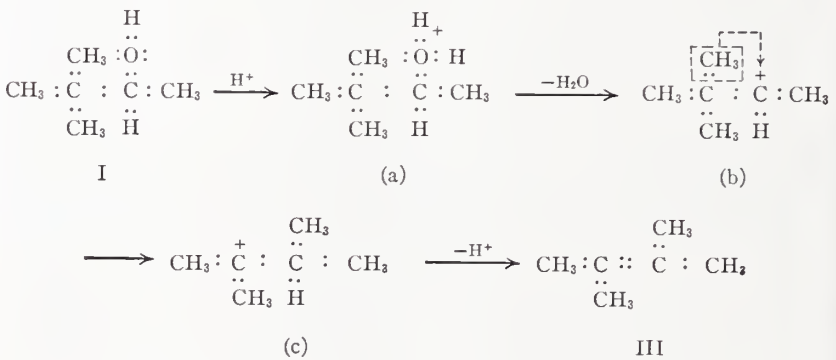
bonium ion (b). This ion is not so stable as the carbonium ion (c), for the charged carbon atom of (b) carries only two alkyl groups

Differential stability of two carbonium ions



(methyl and *t*-butyl), whereas that of (c) carries three (two methyls and an isopropyl); alkyl groups, being electron-releasing, partially balance the positive charge and hence increase stability. The difference in stability of the two carbonium ions provides a driving force for rearrangement of (b) to (c) by migration of a methyl group. Ion (c) then loses a proton (hydrogen atom from one carbon and the positive charge from the other), and the product is tetramethylethylene (III). The electronic formulation of the reaction shows that in both

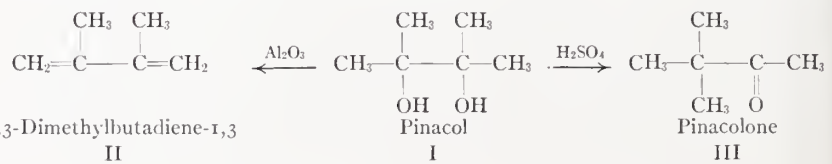
Electronic formulation



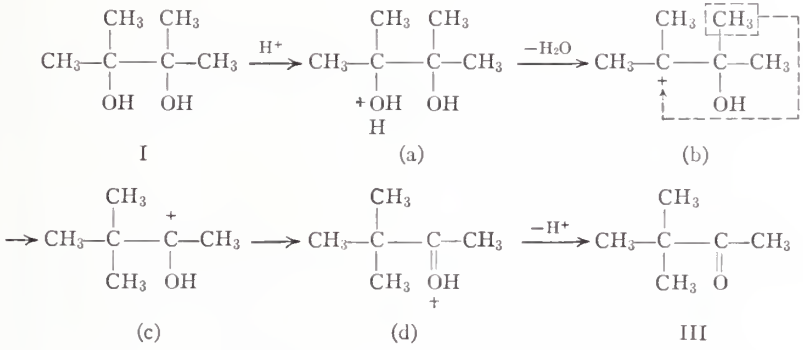
intermediate ions the carbon atom carrying the charge is surrounded by only six electrons and is therefore electron-deficient and reactive. It will be noted also that the methyl group in migrating from one carbon to the other carries with it the pair of shared electrons.

14.4 Pinacol Rearrangement. One of the examples cited earlier in illustration of the method of dehydration of alcohols by distillation

Normal and abnormal dehydration



over alumina (10.3) was that of pinacol (I), available by bimolecular reduction of acetone (12.16). The dehydration proceeds normally and affords 2,3-dimethylbutadiene-1,3 (II) in high yield. On the other hand, if pinacol is refluxed briefly with 30% sulfuric acid it is dehydrated to pinacolone (III). This ketone is a product of a rearrangement involving migration of a methyl group, and the reaction is closely analogous to the Wagner-Meerwein rearrangement discussed above and is interpreted by a similar mechanism. The steps of ac-



I (a) (b) (c) (d) III

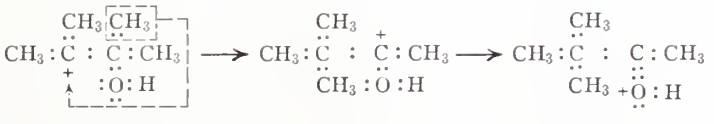
Mechanism of rearrangement

ceptance of a hydrogen ion by oxygen (a) and loss of water to form the carbonium ion (b) are the same as before. In the present case, however, methyl migration with rearrangement of carbonium ion (b) to carbonium ion (c) is occasioned not by a difference in the inductive effects of groups in these ions but because carbonium ion (c) is at once stabilized by a shift of the charge from carbon to oxygen to produce the tremendously more stable oxonium ion (d). Ion (d) then loses a hydrogen ion to form pinacolone, III.

Due to superior stability of oxonium ion (d)

The electronic formulations of the transient ions help explain the process. The charged carbon atom of (c), as of (b), carries only six

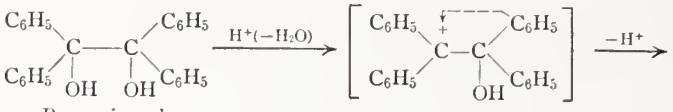
14.5



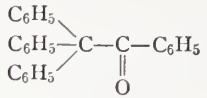
(b) (c) (d)

Ions (b) and (c) electron-deficient

electrons and is hence very unstable, but the charged oxygen in (d) has the full complement of eight electrons, as does the carbon to which it is attached. The driving force for the rearrangement thus comes from the tendency of electron-deficient intermediates to form a stable oxonium ion. Benzopinacol (12.17) when heated in acetic acid with a trace of iodine rearranges in 95% yield to benzopinacolone.



Benzopinacol



Benzopinacolone

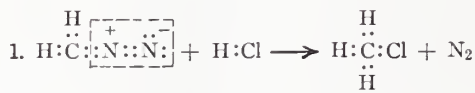
14.6 **Arndt-Eistert Reaction.** — This reaction utilizes the interesting reagent diazomethane, a yellow gas of the formula CH_2N_2. The substance was discovered in 1894 by Hans, Baron von Pechmann, who thought it to be a cyclic azo compound (a) and named it accordingly.

Diazomethane (b)



(a) (b)

Diazomethane was later recognized as a noncyclic, highly unsaturated resonance hybrid of which (b) is one of the contributing structures. von Pechmann found that hydrochloric acid reacts with diazomethane with evolution of nitrogen and formation of methyl chloride. The reaction can be formulated as follows:

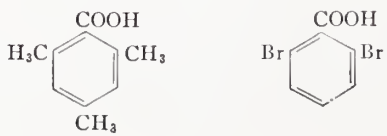


Diazomethane reacts also with carboxylic acids and provides an elegant method for the preparation of methyl esters. When a yellow ethereal solution of the gas is added in portions to a solution or suspension of the acid in ether, nitrogen is evolved at once and the yellow color is discharged. When the color of a fresh portion of reagent is no longer discharged, it is evident that the reaction is complete; the solution is then warmed on the steam bath to expel excess reagent, and a colorless solution of the desired ester results.

Use for esterification

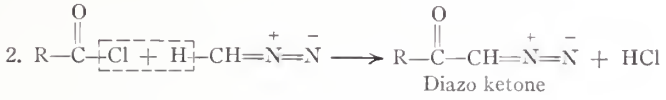
14.7 Methods for the preparation of diazomethane have steadily improved, and the reagent is used widely for esterification in research work; it is too costly for use in the industry. An important application is for esterification of acids too sterically hindered to undergo Fischer esterification. The two acids formulated, for example, remain

Esterification of hindered acids



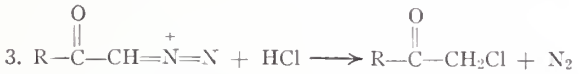
unchanged when refluxed with methanol containing 3% hydrogen chloride but are easily esterified with diazomethane.

The first step in the Arndt-Eistert reaction is condensation of an acid chloride with diazomethane to form a diazo ketone (2). The



2. $R-C(=O)-Cl + H-CH=\overset{+}{N}=\overset{-}{N} \longrightarrow R-C(=O)-CH=\overset{+}{N}=\overset{-}{N} + HCl$

Diazo ketone



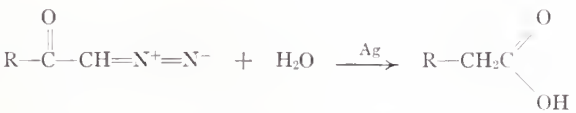
3. $R-C(=O)-CH=\overset{+}{N}=N + HCl \longrightarrow R-C(=O)-CH_2Cl + N_2$

condensation had been investigated in England in 1915, but the product isolated was not the diazo ketone but the chloro ketone (3) formed from it by reaction with the hydrogen chloride liberated in reaction (2). Fritz Arndt and Bernd Eistert in Germany in 1927 recognized this difficulty, noted that the earlier workers had used only one mole of diazomethane and had added the acid chloride to it, and found that by suitable increase in the amount of reagent and by adding the diazomethane slowly to the acid chloride, rather than the reverse, so that the hydrogen chloride formed would be destroyed by reaction with the reagent as in 1, p. 232, diazo ketones can be prepared without difficulty in high yield.

Preparation of a diazo ketone

14.8

In the completing step of the Arndt-Eistert reaction the diazo ketone is heated with water in the presence of colloidal silver as catalyst. The reaction would appear to involve a rearrangement,

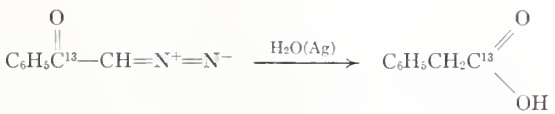


$R-C(=O)-CH=N^+=N^- + H_2O \xrightarrow{Ag} R-CH_2C(=O)-OH$

Completing step

14.9

for the R group initially joined to the carbonyl group is joined in the product to a methylene group. Indeed rearrangement has been proved to occur by an experiment with an isotopically labeled diazo ketone:



$C_6H_5C^{13}(=O)-CH=N^+=N^- \xrightarrow{H_2O(Ag)} C_6H_5CH_2C^{13}(=O)-OH$

A further clue to the mechanism of the reaction is that diazo ketones when decomposed in the absence of water yield ketenes of the formula RCH=C=O. Ketene itself adds acetic acid to form acetic anhydride (9.6), and it adds water to form acetic acid. The carboxylic acid formed when a diazo ketone is decomposed in the presence of water

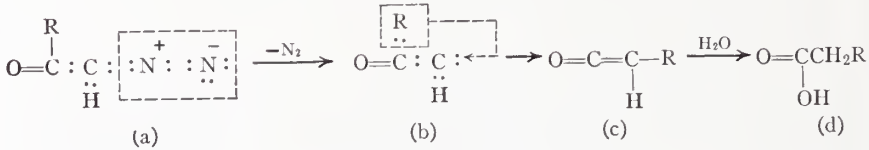
An intermediate ketene

evidently arises by addition of water to the intermediate ketene. With the further knowledge that the carbonyl group of the diazo



ketone becomes part of the carboxyl group of the acid, the reaction can be inferred to take the following course. Loss of nitrogen from

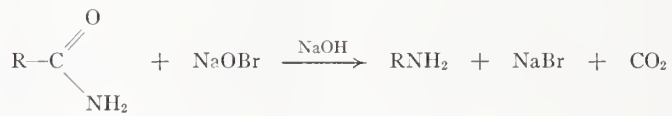
Mechanism of the Arndt-Eistert reaction



the diazo ketone (a) produces the intermediate (b) having an electron-deficient carbon. The alkyl group therefore migrates with the pair of shared electrons to fill the open sextet and give the ketene (c), which adds water to form the acid (d). The Arndt-Eistert reaction is useful in synthesis because it provides a means of lengthening an acid chain: $RCOOH \longrightarrow RCH_2COOH$.

14.10 **Hofmann Reaction.** — In 1881 Hofmann discovered a remarkable transformation of amides brought about by reaction with sodium hypobromite. The carbonyl group of the amide is eliminated and a

Useful route to primary amines



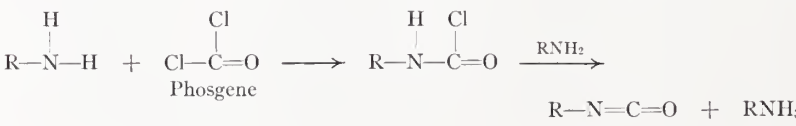
primary amine is formed in high yield and purity. Indeed this is a superior method for preparing primary amines uncontaminated with secondary amines.

14.11 A similarity to the Arndt-Eistert reaction is that in each case an alkyl group linked in the starting material to a carbonyl group appears in the reaction product joined to the adjacent atom, in the present case nitrogen. Furthermore, intermediates have been isolated and characterized as isocyanates, which are structurally similar to

Analogy to Arndt-Eistert reaction

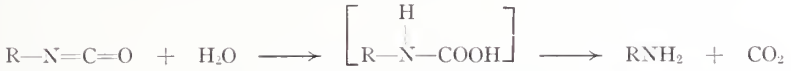


ketenes. The usual method of preparing an isocyanate is by the reaction of an amine with phosgene, the diacid chloride of carbonic acid. An isocyanate, like a ketene, can add water, but in this case the



resulting acid having a carboxyl group linked to nitrogen is unstable and spontaneously loses carbon dioxide.

Preparation and properties of isocyanates

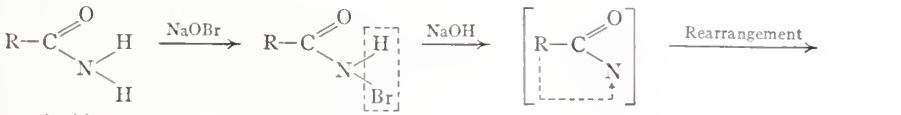


Thus it appears that in the Hofmann reaction the amide is converted into an isocyanate by a rearrangement and that this undergoes hydrolysis to the amine. A further piece of information reveals the nature of the first step. The reagent sodium hypobromite is usually prepared by dissolving bromine in excess alkali. When the amount of alkali is limited to conform to equation 1, the product is the bromoamide, RCONHBr, in which one hydrogen on nitrogen is re-

14.12



placed by bromine. The bromoamide reacts with alkali to give an amine, and hence is indeed an intermediate. When the bromoamide is formed in the presence of excess alkali, it apparently suffers elimination of hydrogen bromide from nitrogen to give an unstable inter-



Reaction mechanism

mediate which rearranges by migration of the alkyl group from carbon to nitrogen to form the isocyanate. The remaining steps then follow the course already described. The electronic formulation shows that the nitrogen atom of the intermediate is electron-deficient and so invites rearrangement.



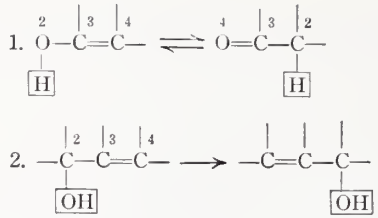
Electron sextet

ALLYLIC REARRANGEMENTS

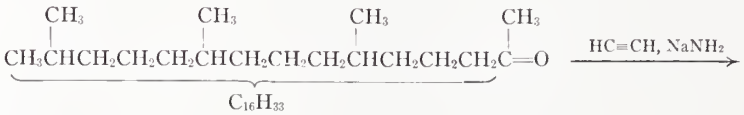
The rearrangements discussed above all involve an intermediate having an electron-deficient atom. Rearrangements of a second type involve rather a process exactly like the familiar 2,4-shift of hydrogen in a 1—2—3=4 system, such as the keto-enol isomerization (1). A similar shift of a hydroxyl group or halogen atom in an allylic alcohol or halide is called an allylic rearrangement. Such rearrangements

14.13

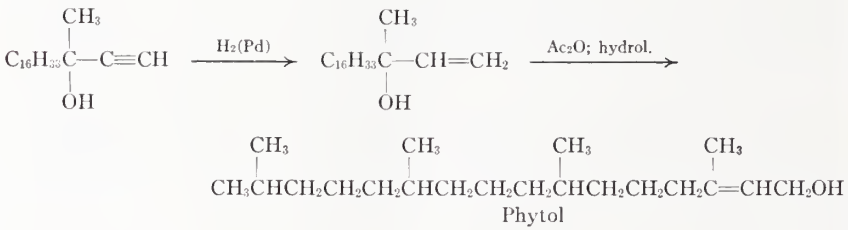
Analogy to keto-enol shift



often proceed very smoothly, particularly if the initial alcohol is tertiary and the rearranged allylic alcohol is primary, for a reason which will be evident from the following example. For the synthesis of the natural product phytol (17.9), the saturated ketone formulated



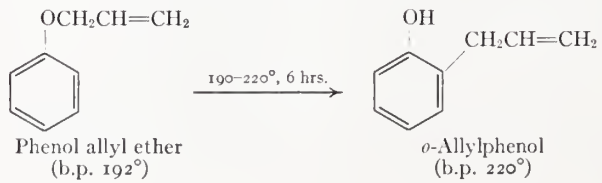
Use in synthesis of phytol



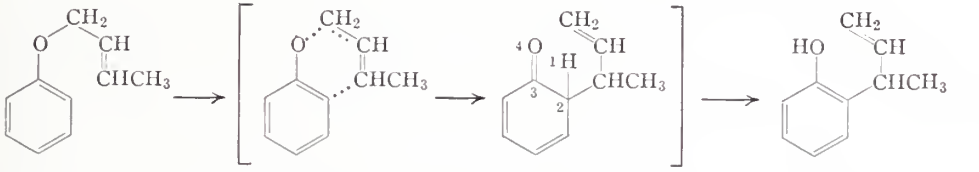
was built up by steps which will not be discussed, and acetylene was added to the carbonyl group in the presence of sodamide. Selective hydrogenation reduced the triple bond to a double bond and thus produced a tertiary allylic alcohol. When warmed with acetic anhydride this substance underwent smooth allylic rearrangement and gave the acetate of phytol, from which phytol itself was obtained by hydrolysis. Both phytol and its precursor are allylic alcohols, but phytol is capable of being acetylated while the tertiary precursor is not. Hence if an equilibrium initially exists between the two alcohols, selective removal of the primary component as the acetate displaces the equilibrium.

Tertiary ⟶ primary (acylable)

14.14 Claisen Rearrangement. — Working in his private laboratory after retirement from a succession of professorships, Ludwig Claisen at the age of 72 discovered that the allyl ether of phenol when merely heated at the boiling point rearranges to give *o*-allylphenol in excellent yield.



The reaction is a general one and has many useful applications. When the allyl group carries a substituent, as in the ether I, the sole product of rearrangement is III, and not the isomer with a terminal



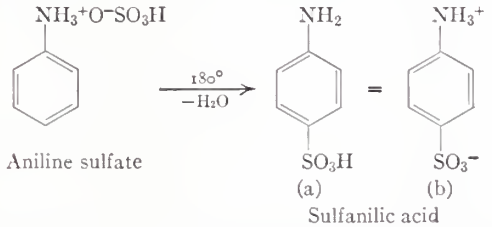
I Transition state II III

Mechanism

methyl group. The reaction thus probably proceeds through a transition state in which the oxygen–carbon bond is weakened and new carbon–carbon bonds have started to form. The initial product presumably is the ketone II which, by a 2,4- or allylic shift of hydrogen, enolizes to resonance-stabilized III.

Side-chain ⟶ Nucleus Rearrangements.—Sulfanilic acid, a useful dye intermediate, is prepared by baking aniline sulfate at 180° until a test portion when neutralized with alkali no longer liberates aniline. The reaction product is represented formally as the aminosulfonic

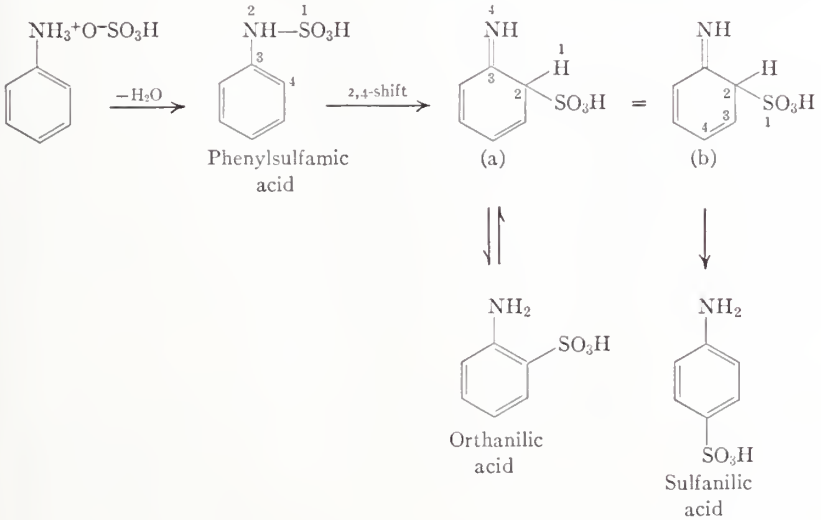
14.15



Aniline sulfate (a) (b) Sulfanilic acid

Sulfanilic acid

acid (a), but actually exists as the dipolar ion (b). Experiments by Eugen Bamberger at Munich established that the initial reaction is

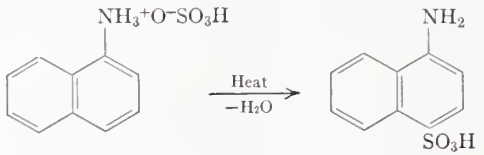


Phenylsulfamic acid (a) (b) Orthanilic acid Sulfanilic acid

Mechanism

loss of water with formation of phenylsulfamic acid, and that this rearranges first to orthanilic acid and then to sulfanilic acid. The progressive migrations to the *ortho* and then the *para* position can be attributed to allylic, or 2,4-shifts. Phenylsulfamic acid affords orthanilic acid by a 2,4-shift of the sulfonic acid group to the ortho position (a), with a similar shift of hydrogen in the reverse direction. Intermediate (a), in equilibrium with orthanilic acid, is numbered as in (b) to show that the sulfonic acid group, by a 2,4-shift, can be displaced to the *para* position to give the more stable sulfanilic acid.

Naphthionic acid

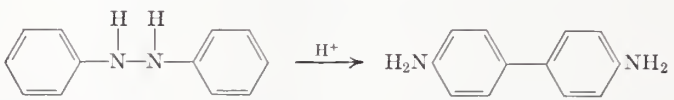


α-Naphthylamine sulfate — Naphthionic acid

The naphthalene analog, naphthionic acid, is prepared by a similar side-chain ⟶ nucleus rearrangement.

14.16 A double rearrangement of the same type is involved in the acid-catalyzed rearrangement of hydrazobenzene, a product of controlled

Benzidine



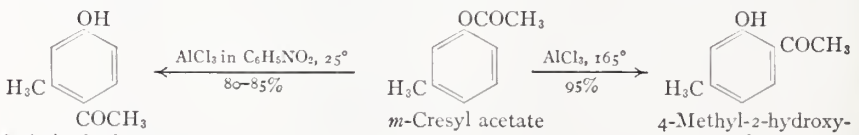
Hydrazobenzene — Benzidine

electrolytic reduction of nitrobenzene, to benzidine. Benzidine, or 4,4′-diaminodiphenyl, is a useful dye intermediate.

FRIES REACTION

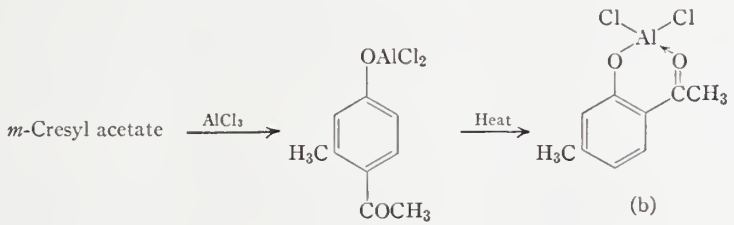
14.17 The Friedel-Crafts reaction is not applicable to a phenol because phenol combines with the catalyst to form an unreactive aluminum chloride derivative: $C_6H_5OH + AlCl_3 \longrightarrow C_6H_5OAlCl_2 + HCl$. However, Karl Fries in Germany discovered that an acetyl group can be introduced by acetylation of the phenol and rearrangement of the acetyl group from oxygen to the nucleus under the catalytic influence of aluminum chloride. The migrating group enters the *ortho* or *para*

Temperature effect



2-Methyl-4-hydroxyacetophenone (m.p. 128°, b.p. 313°) — *m*-Cresyl acetate — 4-Methyl-2-hydroxyacetophenone (m.p. 21°, b.p. 245°)

position, and the *o* / *p* ratio is highly dependent on the reaction temperature. Thus *m*-cresyl acetate at a low temperature yields chiefly the *p*-isomer and at a high temperature it gives almost exclusively the *o*-isomer. The result appears odd, for in an ordinary Friedel-Crafts reaction the entering group avoids the *o*-position, particularly at a high temperature. Furthermore, the relative stability of the isomers appears to be just the reverse that of orthanilic and sulfanilic acid. The facts are explained as follows. The substances present in the reaction mixtures are not the free phenols formulated above, but the



aluminum chloride derivatives (a) and (b), and the *ortho* derivative (b) is stabilized by a special effect known as chelation (Gr. *chēlē*, claw). The carbonyl oxygen is bonded to aluminum by a coordinate link like that in a hydrogen-bonded alcohol dimer (2.38). The link to aluminum is stronger than a link to hydrogen, and it closes a ring of six members and of maximal stability. The *p*-derivative (a) can form no stabilizing chelate ring and hence this substance, the normal product of reaction at a low temperature, is isomerized by heat to (b), from which the *o*-aceto compound is liberated on reaction of the derivative with water.

***o*-Derivative stabilized by chelation**

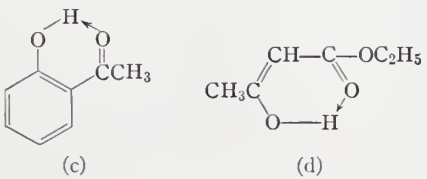
The migration of the acetyl group from oxygen to the *p*-position in the low-temperature reaction evidently does not proceed by a series of allylic shifts, analogous to the formation of sulfanilic acid, for then the stable *o*-derivative (b) would be the initial product. Probably the reaction is not intramolecular but rather involves attack by the aceto group of one molecule on the *p*-position of a second molecule.

14.18

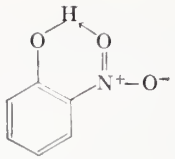
Reaction is intermolecular

Chelation is possible also in a free *o*-hydroxy ketone by hydrogen bonding (c), and this effect undoubtedly accounts for the striking

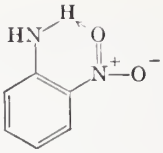
14.19



Other examples of chelation



(e)



(f)

difference in boiling point of the two reaction products from *m*-cresyl acetate formulated above: *para*, 313°; *ortho*, 245°. The chelated *o*-isomer has diminished hydroxylic character and hence is considerably more volatile (and more soluble in ligroin) than the isomer. Similar chelation in the enol form of ethyl acetoacetate (d), but not in the keto form, accounts for the observation that when the equilibrium mixture containing only 7% enol is distilled very slowly the distillate consists almost exclusively of the evidently more volatile enol form. *o*-Nitrophenol (e) and *o*-nitroaniline (f) also are evidently chelated, since they are both volatile with steam whereas the *p*-isomers are not.

SUMMARY

Electron-Deficient Intermediates

n-Propyl ⟶ isopropyl rearrangement in Friedel-Crafts alkylation attributed to greater stability of the secondary carbonium ion:

$$CH_3CH_2\overset{+}{C}H_2 \longrightarrow CH_3\overset{+}{C}HCH_3.$$

Wagner-Meerwein rearrangement. Dehydration of $(CH_3)_3C{-}CH(OH)CH_3$ over Al_2O_3 proceeds normally. Acid-catalyzed dehydration gives rearranged product $(CH_3)_2C{=}C(CH_3)_2$. Mechanism: protonation of oxygen, loss of water to give a carbonium ion; this is stabilized by only two electron-releasing alkyl groups, and hence rearranges to an ion having three such groups, which loses a proton to form the rearranged alkene. In both ions the charged carbon atom is electron-deficient (shell of 6, not 8).

Pinacol, $(CH_3)_2C(OH)C(OH)(CH_3)_2$, gives dimethylbutadiene when distilled over alumina but on dehydration with H_2SO_4 a methyl group migrates and the product is pinacolone, $(CH_3)_3CCOCH_3$. An initially formed carbonium ion is induced to rearrange to another such ion because the latter is at once stabilized by shift of the charge from carbon to oxygen to give a stable oxonium ion.

Arndt-Eistert reaction utilizes diazomethane, $CH_2{=}\overset{+}{N}{=}\overset{-}{N}$, a yellow gas very useful for esterification of carboxylic acids. Di-*o*-substituted benzoic acids too hindered to be esterified by the Fischer method are easily esterified with diazomethane.

Diazo ketones readily prepared by addition of excess diazomethane to a solution of an acid chloride:

$$RCOCl + 2\ CH_2{=}N^+{=}N^- \longrightarrow RCOCH{=}N^+{=}N^- + CH_3Cl + N_2.$$

The rearrangement: $RCOCH{=}N^+{=}N^- + H_2O$ (Ag) ⟶ RCH_2CO_2H. A test with an isotopically labeled diazo ketone proves that R migrates to the adjacent carbon. Further evidence is that in the absence of water the product is a ketene, RCH=C=O, which adds water to give RCH_2CO_2H. Mechanism: loss of nitrogen to give R(O=)CCH (carbon with an electron sextet); migration of R to give O=C=CHR; $+ H_2O$ ⟶ HO(O=)CCH_2R.

Hofmann reaction:

$$RCONH_2 + NaOBr \longrightarrow RNH_2.$$

Clues to mechanism: (1) R initially joined to C appears on the adjacent N (cf. Arndt-Eistert reaction); (2) isolation of an intermediate isocyanate, R—N=C=O (cf. $R_2C{=}C{=}O$, a ketene); isocyanates known to be hydrolyzed thus:

$$RN{=}C{=}O + H_2O \longrightarrow RNHCOOH \longrightarrow RNH_2 + CO_2;$$

(3) in the absence of excess alkali an amide yields a stable bromo ketone. Mechanism:

$$RCONH_2 \longrightarrow RCONHBr \longrightarrow$$
$$RC(=O)N \text{ (nitrogen with only 6 electrons)} \longrightarrow O{=}C{=}N{-}R \longrightarrow H_2NR.$$

Allylic Rearrangements

Rearrangement of one allylic alcohol to another by a 2,4-OH shift analogous to enol ⟶ keto 2,4-H shift. If the initial alcohol is tertiary and the rearranged alcohol primary, rearrangement proceeds smoothly in acetic anhydride solution because the primary alcohol is removed from the equilibrium as the acetate (*t*-alcohols not being acylable).

Claisen rearrangement of phenol allyl ether:

$$C_6H_5O\overset{\alpha}{C}H_2\overset{\beta}{C}H{=}\overset{\gamma}{C}H_2 \longrightarrow o\text{-}CH_2{=}CHCH_2C_6H_4OH.$$

Evidence that the γ-carbon is the one which becomes attached to the ring: $C_6H_5OCH_2CH{=}CHR \longrightarrow o\text{-}CH_2{=}CHCH(R)C_6H_4OH$. Postulate of a cyclic transition state.

Sulfanilic acid:

$$H_2NC_6H_4SO_3H\text{-}p = H_3N^+C_6H_4SO_3^-\text{-}p.$$

Baking of aniline sulfate at 180° causes dehydration to phenylsulfamic acid ($C_6H_5NHSO_3H$). The SO_3H then migrates to the *o*-position by a 2,4-shift and H moves to N by a 2,4-shift to produce orthanilic acid. By similar shifts the SO_3H migrates to *p*-position to produce sulfanilic acid.

Naphthionic acid, the naphthalene analog, obtained similarly from α-naphthylamine sulfate.

Double rearrangement of same type:

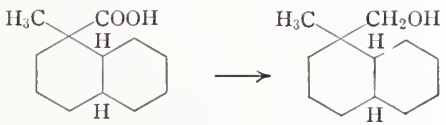
hydrazobenzene ($C_6H_5NHNHC_6H_5$) ⟶
benzidine ($p\text{-}H_2NC_6H_4{-}C_6H_4NH_2\text{-}p'$).

Fries Reaction

Friedel-Crafts reaction not applicable to phenol, since $C_6H_5OH + AlCl_3 \longrightarrow C_6H_5OAlCl_2 + HCl$. However phenyl acetate, $C_6H_5OCOCH_3$, rearranges under the influence of $AlCl_3$ to the *o*- and *p*-aceto derivatives of $C_6H_5OAlCl_2$ (Fries reaction). The *p*-derivative, $CH_3COC_6H_4OAlCl_2\text{-}p$, is the normal product and predominates at a low temperature (25°); it is decomposed by water to $CH_3COC_6H_4OH\text{-}p$. At 165° the aceto group migrates to the *o*-position under the driving force of formation of a stable chelate ring (6-membered; carbonyl oxygen coordinated with Al). Chelation increases volatility. Examples: $o\text{-}CH_3COC_6H_4OH$, $o\text{-}NO_2C_6H_4OH$, $o\text{-}NO_2C_6H_4NH_2$, enol form of ethyl acetoacetate.

PROBLEMS

1. Note that, in the Wagner-Meerwein rearrangement discussed in 14.2, the alcohol I has a tertiary carbon atom (one carrying three alkyl groups) adjacent to that carrying the hydroxyl group. Neopentyl alcohol, $(CH_3)_3CCH_2OH$, which has the same structural feature, is incapable of undergoing normal dehydration but on treatment with sulfuric acid it eliminates water and an alkene C_5H^{10} is formed. The reaction involves a Wagner-Meerwein rearrangement; see if you can infer the nature of the rearrangement and the structure of the alkene formed.
2. The acid I is difficult to esterify by the Fischer method.



I II

(*a*) How could you prepare the methyl ester of I?
(*b*) How could I be reduced to II?
(*c*) What would you expect to happen on treatment of II with sulfuric acid?

3. The Curtius reaction involves decomposition of an acyl azide in the presence of alkali with formation of a primary amine.

$$R{-}\overset{\overset{O}{\|}}{C}{-}N{=}N^+{=}N^- \xrightarrow{H_2O(NaOH)} RNH_2 + N_2 + CO_2$$

Acyl azide

An acyl azide is similar in structure to a diazo ketone (14.9), and the end product is the same as that produced in the Hofmann reaction (14.12). These analogies should suggest a mechanism for the Curtius reaction.

4. Formulate the following reaction sequence: reaction of cyclohexanone with acetylene, partial hydrogenation (Raney Ni) with uptake of one mole of H_2, reaction with acetic anhydride, hydrolysis.
5. The allyl ether (I) of the enol form of ethyl acetoacetate when heated at the boiling point

$$\begin{array}{l} CH_3C{=}CHCOOC_2H_5 \\ \quad\quad | \\ \quad OCH_2CH{=}CH_2 \end{array}$$

I

undergoes smooth rearrangement to an isomer. What is its structure?

6. Formulate the reaction of the acetate of α-naphthol with aluminum chloride at 25° and at 165°.
7. If isotopically labeled benzoic acid, $C_6H_5C^{13}O_2H$, is to be converted into the methyl ester, the high cost of the starting material dictates use of a method capable of affording the ester in maximal yield. Would the diazomethane method have any advantage over Fischer esterification?
8. Phthalimide is partially hydrolyzed (see Chapter 9, question 7c), the product treated with bromine in excess alkali, and the solution is acidified. What is the reaction product?

CHAPTER 15

OPTICAL ISOMERISM

15.1

Ordinary white light consists of rays of different wave length vibrating in many planes. Light from a special source, such as a sodium lamp, is made up of rays of a single wave length but still vibrating in many planes; it is called monochromatic light. In 1808 the French physicist Malus discovered that light that has passed through a transparent crystal of Iceland spar, a variety of calcium carbonate found in Iceland, differs from normal light in being polarized in a single plane determined by the orientation of the crystal. Experimentation with plane polarized light is simplified by use of the Nicol prism, especially constructed from Iceland spar (William Nicol, Edinburgh). A rough analogy to the operation of a Nicol prism is that a closed book will permit easy insertion of a table knife between the pages only when the knife is held in a specific plane.

Polarized light

Nicol prism

15.2

Further investigation of the interesting phenomenon led to the discovery that a quartz crystal, suitably cut and oriented, when traversed by plane polarized light rotates the plane of polarization. Some crystals turn the beam of polarized light to the right whereas others turn it to the left. The direction of rotation was then correlated with the form of the crystals. Some quartz crystals have a set of faces arranged in a right-handed sense, and others have the same set of faces arranged in a left-handed sense, as shown in Fig. 15.2. Crystals

Rotation of plane polarized light

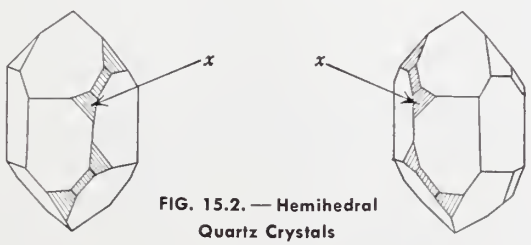


FIG. 15.2. — Hemihedral Quartz Crystals

of these two types rotate plane polarized light in opposite directions. The two crystals are described as hemihedral, which means that each has just half the faces required for symmetry. A pair of hemihedral crystals such as the two shown are described as enantiomorphous, from the Greek *enantios* meaning opposite; this designation refers to the fact that one bears the relationship to the other of the right to the left hand, or of an object to its mirror image.

15.3

Rotation of plane polarized light by hemihedral crystals is a phenomenon in the realm of physics. However, in 1815, the French physicist Biot discovered that certain naturally occurring organic compounds can rotate plane polarized light in solution and recognized that this property must be inherent in the molecules of the dissolved substance. Substances that rotate plane polarized light are said to be optically active. Those that rotate to the right, or clockwise, are defined as dextrorotatory (positive) and those rotating in the opposite direction are levorotatory (negative).

Optical activity in solution

15.4

Polarimeter. — The extent of rotation for a given amount of material can be determined with a polarimeter. This instrument contains two Nicol prisms traversed by a beam of monochromatic light. One, the polarizer, is mounted in a fixed position and transmits plane polarized light to a tube of known length with glass windows at the two ends, in which the solution to be examined is placed. The second Nicol prism, the analyzer, is mounted on a movable axis and can be rotated as desired; the angle of rotation is measured on a circular scale. The zero point on the scale is that which, with the polarimeter tube empty, permits maximum transmission of light, an indication

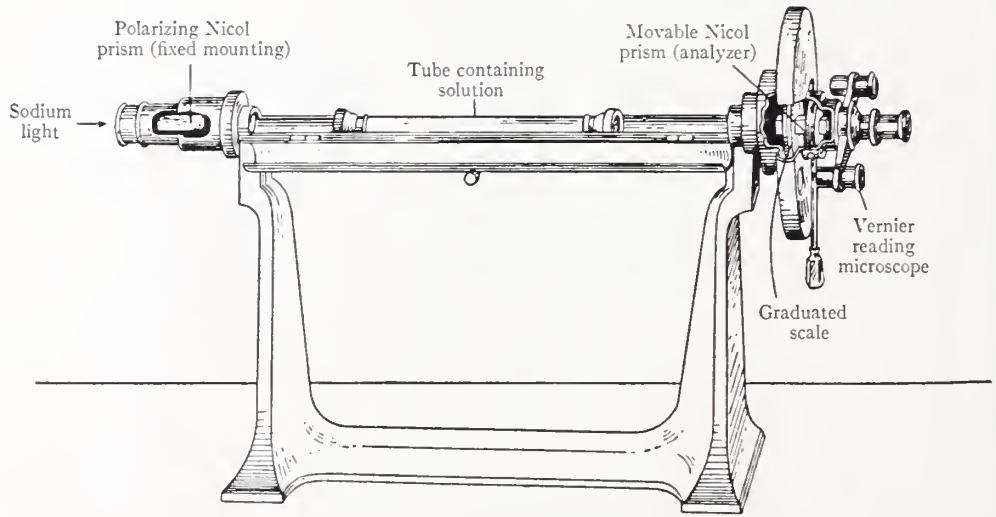


FIG. 15.4. — Polarimeter

that the analyzer has been oriented in the same optical plane as the polarizer; if the analyzer is now turned through an angle of 90°, a point of minimum light transmission is reached, and the Nicols are said to be crossed. When a solution of an optically active substance is placed in the polarimeter tube, light transmitted by the polarizer is rotated to a certain extent either to the right or to the left; light reaching the eyepiece is thus diminished in intensity, but by rotating the analyzer a point can be found where the original intensity is restored and at which the analyzer is aligned with the plane of light emerging from the polarimeter tube; the angle of rotation in either the dextro or levo sense is read from the scale. Results are reported in terms of the specific rotation, $[\alpha]$, defined as the rotation in degrees due to a solution containing 1 g. of substance in 1 ml. of solution examined in a 1-decimeter polarimeter tube. Cane sugar is dextrorota-

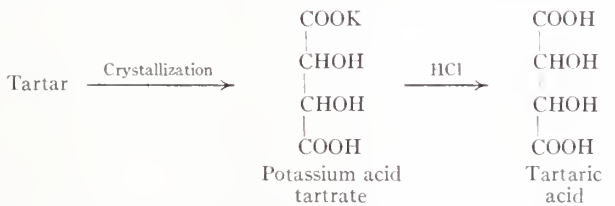
$$[\alpha] = \frac{\text{Observed rotation}}{\text{Length of tube in dm.} \times \text{concentration (g. per ml.)}}$$

Specific rotation

tory in aqueous solution, and the specific rotation measured with the D-line of the sodium spectrum at 20° is reported thus: $[\alpha]_D^{20^\circ} = +66.5^\circ$.

Work of Pasteur. — Following Biot's discovery, chemists in the early part of the 19th century routinely examined new compounds for optical activity. Those made completely by synthesis invariably were found to be optically inactive. Substances derived from plants and animals did not all prove to be optically active, but a considerable number did possess this property. One of the compounds found by Biot to be optically active is tartaric acid, available from the wine industry. The structure of tartaric acid was unknown at the time;

15.5



Tartaric acid optically active

actually it is a dibasic acid of the structure shown. It is present in grape juice as the potassium acid salt, and as the sugar in the juice ferments to alcohol, the alcohol decreases the solubility of the salt and causes it to separate as a sludgy precipitate called tartar. Purification of the salt by crystallization followed by acidification gives tartaric acid. A by-product of the purification was studied in 1831 by Berzelius and named racemic acid (Latin *racemus*, grape). Berzelius recognized that both tartaric and racemic acid have the formula $C_4H_6O_6$, but no other relationship between the two substances had been established or suspected. Indeed, Biot had found tartaric acid

Racemic acid inactive

and its salts to be dextrorotatory and racemic acid and its salts optically inactive.

15.6

Pasteur's crystallographic study

In 1848 Louis Pasteur, on completion of the curriculum at the École Normale in Paris at the age of twenty-six, sought to strengthen his knowledge of crystallography by repeating a series of careful measurements published a few years earlier on the crystalline forms of various salts of tartaric acid. Pasteur's determinations agreed substantially with those reported previously, but as the work proceeded he noticed a very interesting fact that had escaped his predecessor, namely, that all tartrates show undoubted evidence of hemihedral faces. The phenomenon is frequently obscured by irregular development of the crystals, by chance deformations, or by arrestment of the development of faces, but nevertheless Pasteur, by repeating crystallizations where necessary under modified conditions, established that every one of nineteen tartrates investigated exhibits hemihedral faces. A further observation that seemed significant was that the tartrates are all hemihedral in the same sense or direction; this seemed consistent with the fact that they are all optically active in the same sense.

Tartrates found hemihedral

Apparent inconsistency

However, an apparently inconsistent observation had been reported by Mitscherlich, a prominent crystallographer and chemist. Mitscherlich had made a crystallographic comparison of the sodium ammonium salts of optically active tartaric acid and of optically inactive racemic acid and had reported that the two salts have identical crystalline forms. According to Pasteur's observations, the tartrate should be hemihedral and the racemate symmetrical. He therefore reinvestigated the two salts, and found that sodium ammonium tartrate affords hemihedral crystals, like all other tartrates previously studied, but discovered to his great surprise that sodium ammonium racemate is hemihedral also. He then observed that "the hemihedral faces which in the tartrate were all turned the same way were in the racemate inclined sometimes to the right and sometimes to the left." Pasteur carefully picked out a quantity of crystals that were hemihedral to the right and a further quantity of those hemihedral to the left and examined their solutions separately in the polarimeter; he thereupon made the exciting observation that the former material rotated the plane of polarized light to the right and the latter to the left. When equal weights of the two kinds of crystals were dissolved in water, the solution of the mixture, like the starting material, was indifferent to polarized light. In this experiment, conducted in 1848, Pasteur had for the first time achieved the resolution of an optically inactive compound into the component, optically active parts.

Crystals hemihedral in opposite senses

15.7

By precipitation of the barium salt of each substance and digestion with sulfuric acid, the free acids were obtained. One proved identical

with the natural, dextrorotatory tartaric acid, or *d*-tartaric acid, whereas the other was a heretofore unknown substance exhibiting rotation to the same extent in the opposite direction and hence called the *levo* acid, or *l*-tartaric acid. Both *d*- and *l*-tartaric acid have the same melting point, solubility in a given solvent, dissociation constant, and density, and they exhibit the same chemical behavior. In fact the two substances are identical with the exception that they rotate the plane of polarized light in opposite directions (but to the same extent) and that they form crystals that are hemihedral in the opposite sense.

Discovery of l-tartaric acid

15.8

It was recognized only some time later that the resolution achieved by Pasteur is dependent upon a critical temperature factor. If sodium ammonium racemate is crystallized from a hot concentrated solution, the crystals separating have the same form and are symmetrical; they show no sign of hemihedrism. In this case each crystal contains equal parts of the *dextro* and the *levo* form and is optically inactive; the racemate salt is a molecular compound having the analysis of a monohydrate, $Na(NH_4)C_4H_4O_6 \cdot H_2O$. It is only when crystals separate at a temperature below a critical transition point of 28° that hemihedral crystals composed respectively of molecules of the *dextro* and the *levo* salt separate side by side to give a crystal mixture known as a conglomerate; this consists of crystals of sodium ammonium *d*-tartrate and sodium ammonium *l*-tartrate, both of which are tetrahydrates: $Na(NH_4)C_4H_4O_6 \cdot 4\,H_2O$. Pasteur had adopted a technique of slow crystallization from a very dilute solution and thereby had the good fortune to have operated at a temperature below the transition point, whereas previous investigators evidently had conducted crystallization at higher temperatures and had obtained only the inactive racemate. The initial resolution accomplished in 1848 is particularly remarkable because of the rarity of such instances; in a century of subsequent research, only nine other examples have been encountered in which crystallization at any temperature affords a conglomerate of sufficiently large crystals displaying hemihedry to permit their segregation by hand picking under a lens.

Transition temperature of crystallization

15.9

The relationship between the crystals of *d*- and *l*-tartaric acid is the same as that illustrated in Fig. 15.2 for right- and left-handed quartz crystals. The two are similar but not superposable, and the one is to the other as an object is to its mirror image; the crystals are thus asymmetric, for they possess no plane of symmetry. In an interpretation of the new phenomenon, now described as optical isomerism, Pasteur concluded that the tartaric acids must possess asymmetry within the molecule itself. Although the concept of structural formulas was developed only many years later, Pasteur

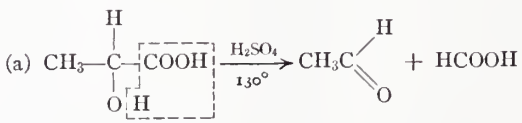
had the vision to foresee the need of something beyond structural formulas for full understanding of organic compounds. He recognized that two substances identical in composition may differ in the arrangement of the atoms in space and envisioned arrangements showing asymmetry in opposite senses. "Are the atoms of the *dextro* acid grouped on the spirals of a right-handed helix," questioned Pasteur in 1860, "or situated at the corners of an irregular tetrahedron, or have they some other asymmetric grouping? We cannot answer these questions. But it cannot be a subject of doubt that there exists an asymmetric arrangement having a nonsuperposable image. It is not less certain that the atoms of the *levo* acid possess precisely the inverse asymmetric arrangement."

Pasteur's conclusion

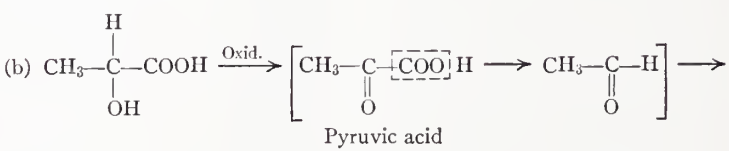
15.10 Isomerism of the Lactic Acids. — Scheele (1780) discovered in sour milk a substance which he called lactic acid and which subsequently was found to arise by bacterial fermentation of milk sugar (lactose). Berzelius (1807) discovered another lactic acid of the same composition as a constituent of muscle tissue. After the advent of the structural theory of Kekulé (1859), Johannes Wislicenus at Zurich undertook an extensive investigation of the two lactic acids. When each acid is pure, the only difference discoverable is their behavior to plane polarized light: one is dextrorotatory and the other levorotatory. They are identical in all other physical properties and are indistinguishable in chemical behavior. Degradations indicated that they both have the same structure, that of α-hydroxypropionic acid. Thus each acid is cleaved by concentrated acid to acetaldehyde and formic

d- and l-Acids

Structures the same



Lactic acid (*d*-or *l*-)



Pyruvic acid

$$CH_3COOH + CO_2 + H_2O$$

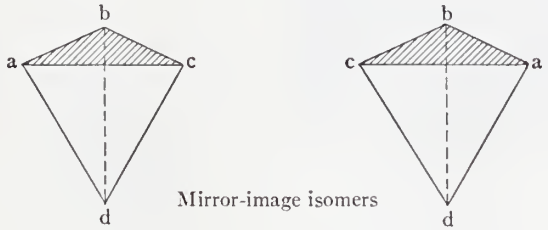
acid (a), and each is oxidized to pyruvic acid and then to acetic acid (b). Synthesis by addition of hydrogen cyanide to acetaldehyde and hydrolysis of the cyanohydrin gives a lactic acid which is optically inactive but identical in chemical properties with *d*- and *l*-lactic acid. At the conclusion of his experiments of 1873, Wislicenus wrote: "If molecules can be structurally identical and yet possess dissimilar

Conclusion of Wislicenus

properties, this difference can be explained only on the ground that it is due to a different arrangement of the atoms in space."

Optical Isomerism 15.11

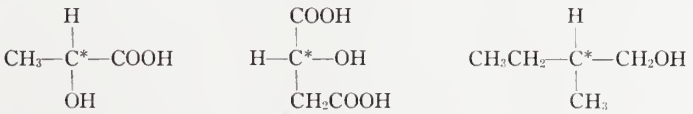
Theory of van't Hoff and Le Bel. — A theory which met the requirements envisioned by Pasteur and set forth clearly by Wislicenus twenty-five years later, was announced independently in 1874 by van't Hoff in Holland (September) and by Le Bel in France (November). The theory, already outlined (1.25), states that the four valences of carbon are directed to the corners of a tetrahedron, at the center of which the carbon atom is situated. If four different atoms or groups are attached at the four corners, then the molecule *Cabcd* is asymmetric and can exist in two forms. The three-dimensional models



Mirror-image isomers

cannot be superposed upon each other and hence are different, even though they represent the same structural arrangement of atoms. They bear a relationship to each other corresponding to that which exists between right- and left-handed quartz crystals, or between an object and its mirror image. A tetrahedral carbon atom carrying four different groups therefore must invariably constitute a center of asymmetry and permit two arrangements in space. This asymmetry allows for existence of two isomers identical in all respects except optical properties. Asymmetry is possible only if all four valences of carbon are utilized by different groups; for example, if the substituent *c* in the above space formulas is replaced by a second *a* group, the formulas become identical.

The central carbon of lactic acid carries four substituents that are all different and hence is asymmetric, as indicated in the formula by an asterisk. The structure of malic acid was known, and the presence 15.12



Compounds with asymmetric carbon

of an asymmetric carbon atom accounted for the optical activity of the substance. One of the amyl alcohols had been isolated from a natural source and called "active" amyl alcohol because of its optical activity. Note that the central carbon is flanked on each side by a methylene group but that it is nevertheless asymmetric since one



Jacobus Hendricus van't Hoff, 1852–1911
Born Rotterdam, Holland; Ph.D. Utrecht; professor at the University of Amsterdam; Nobel Prize 1901

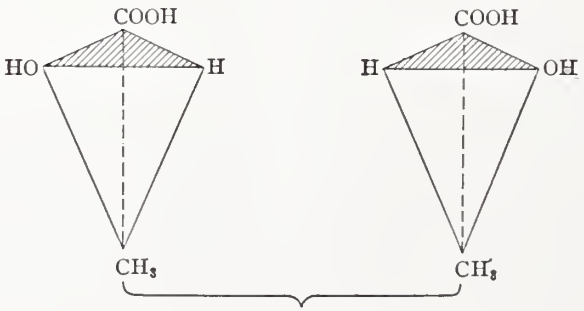
methylene is part of an ethyl group and the other a part of the group —CH_2OH. Thus consideration must be given to the entire group attached. Not very many more optically active compounds of established structure were known when van't Hoff and Le Bel advanced their theory, and their ideas met with considerable opposition in some quarters. Within a decade, however, those few observations that had appeared contradictory to the theory were shown to be in error (e.g., supposed activity of propyl alcohol, due to contamination with amyl alcohol) and abundant new evidence was accumulated in substantiation of the concept. van't Hoff turned to physical chemistry and eventually won the Nobel Prize for outstanding contributions in this field. However, in 1883 he wrote a booklet entitled "Ten Years in the History of a Theory," in which he summarized what had been established and predicted all the main facts and relationships about optical isomerism that are now known. He foresaw the then unknown phenomenon of geometrical isomerism, and by 1887 this further prediction was verified.

Theory substantiated

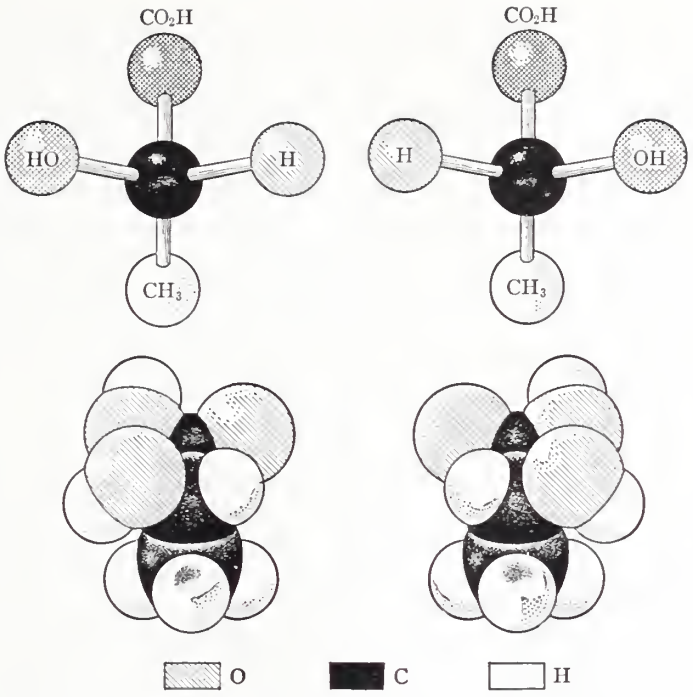
van't Hoff's predictions

15.13 Compounds with One Asymmetric Carbon. — Three sets of repre-

Space formulas



d- and *l*-lactic acids



Models

Stuart models

sentations are shown for depicting the spatial arrangement, or configuration, of *d*- and *l*-lactic acid: space formulas, ball-and-stick models, and Stuart models. Whatever models or formulas are used, each form of lactic acid is seen to be asymmetric, since it possesses no plane of symmetry, or since the two forms are like right- and left-handed screws. Because such mirror-image isomers bear the relationship to each other of enantiomorphous crystals of quartz or of sodium ammonium racemate, they are described as a pair of enantiomers. In all instances where the *d*- and *l*-forms have been isolated in satisfactory purity, the physical constants of the enantiomers are the same within experimental error. This concordance is illustrated by data given in Table 15.13 for the optically active mandelic acids. Although the enantiomers melt at the same temperature, a mixture of a small amount of the *d*-acid depresses the melting point of the *l*-form, and vice versa; hence the method of mixed melting-point determination

Enantiomers

TABLE 15.13

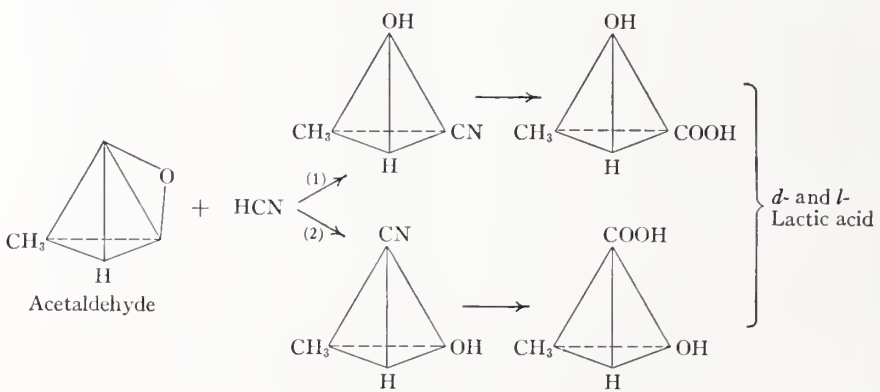
MANDELIC ACIDS, $C_6H_5CH(OH)COOH$

	M.P., °C.	Solubility, g./100 g. $H_2O^{20°}$	Acidic dissociation, $pK_a^{25°}$	Specific rotation, $[\alpha]_D^{20°}$ 2% in H_2O
d-Acid	132.8	8.54 g.		+ 155.5°
l-Acid	132.8	8.64 g.	3.37	− 154.4°
dl-Acid	118.5	15.97 g.	3.38	inactive

detects even a subtle difference. That the melting point of the *dl*-acid, or racemic form, is below the melting points of the component acids is purely fortuitous, for such molecular compounds can have properties not predictable from those of the component parts. Relative solubilities are likewise unforetellable. The acidic dissociation constant is a property of the dissolved molecules and is independent of the characteristics of the solid materials, and the fact that the *dl*-acid has the same value as that found for the *l*-acid is evidence that the enantiomers correspond in acidity. Chemical properties are also independent of the physical forms, and the *d*-, *l*-, and *dl*-acids exhibit the same chemical characteristics; they react in the same way with the same reagents, and the reactions proceed at the identical rate in the three cases. Correspondence in physical properties is accounted for by any of the models illustrated, for in each enantiomer the same groups are present and have the same spatial relationship to one another and to the asymmetric carbon atom. If any attractions or repulsions between groups are manifested in one form, they are equally operative in the other.

Properties of d-, l-, and dl-acids

15.14 Synthesis. — The lactic acid obtained from acetaldehyde by the cyanohydrin synthesis is optically inactive and is a *dl*-modification. Indeed any synthesis of a compound having a single asymmetric carbon atom yields a *dl*-form or racemate; that is, it affords the same number of *d*- and of *l*-molecules. A simple explanation is found in the van't Hoff-Le Bel theory. If acetaldehyde is represented by a space formula in which the carbon atom of the carbonyl group is



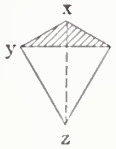
dl-Product by law of probability

indicated by a tetrahedron with methyl at one corner and hydrogen at another and with the other two corners united to oxygen by a double link, the molecule has a plane of symmetry bisecting the oxygen atom and the hydrogen and methyl substituents. This symmetry means that there is no difference in the two linkages of the carbonyl group, and hence that in the reaction with hydrogen cyanide the same

opportunity exists for opening of one linkage as of the other, (1) and (2). Since an experiment on even a microscale involves many millions of molecules, the law of the probability of occurrence of two equally likely events is applicable with accuracy, and the carbonyl group must open, on the average, to an equal extent in the two possible directions. Asymmetry is established in the initial addition; the two enantiomeric cyanohydrins are formed in equal amounts, and equal amounts of the *d*- and *l*-acids result on hydrolysis.

Correlations and Conventions. — If a weakly dextrorotatory acid of the type formulated is converted into the methyl ester, the acid

15.15

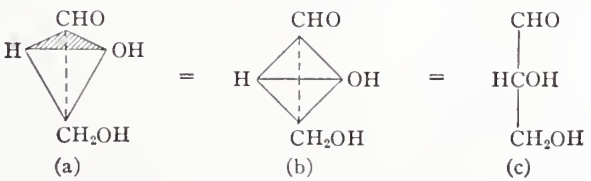


COOH ($COOCH_3$, COCl, $CONH_2$, COC_6H_5)

chloride, amide, or phenyl ketone derivative, there is no assurance that all of these derivatives will also be dextrorotatory. Indeed cases are known where some derivatives are dextrorotatory and others are levorotatory, even though they all have been correlated and are known to belong to the same stereochemical series. E. Fischer (1891) established the convention of indicating a stereochemical series with a small capital roman D or L. The designations *d*- or *l*- thus refer only to the direction of rotation of a compound and can be replaced, if desired, by the designations (+)- and (−)-. As a reference standard for the D-series, Fischer chose natural, dextrorotatory glyceraldehyde, $HOCH_2CH(OH)CHO$; the description of this substance as D-(+)-glyceraldehyde means that it belongs to the D-stereochemical series and has a positive (*dextro*) rotation. The opposite configuration is designated L. D-Glyceraldehyde, in the Fischer convention, is oriented in a perspective tetrahedral model (a) or the equivalent, symmetrically oriented model (b). In both (a) and (b) the solid line connecting H and OH represents an edge of the tetrahedron that projects in front of or above the plane of the paper, and the dotted line connecting CHO and CH_2OH is an edge of the tetrahedron that would be unseen in an opaque mechanical model. For convenience in writing and printing, Fischer defined the following convention for planar pro-

D- and L-series

Planar projection according to Fischer

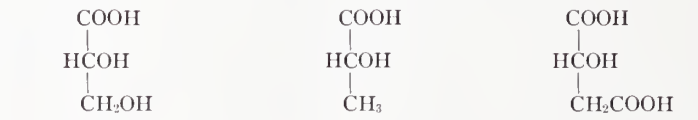


D-(+)-Glyceraldehyde

Reference standard

jection of the three-dimensional model: the model is oriented as in (b) with the carbon chain vertical and to the rear and the hydrogen and hydroxyl standing out in front; the model is then imagined to be flattened and the groups are laid on the plane of the paper in the order that they appear in the model, as in (c). The planar projection (c) must be thought of in terms of the actual model that it represents (H and OH extending toward the front); it can be turned around in the plane of the paper, but must not be imagined to be lifted and inverted. If the carbon chain contains two or more adjacent asymmetric carbon atoms (see tartaric acid, below), the projection is made in the same way from a model oriented with CHO or equivalent group at the top, CH_2OH or equivalent at the bottom, the carbon chain vertical and to the rear, and H and OH groups extending to the front.

15.16 Any compound that has been shown to contain an asymmetric carbon atom of the same configuration as that of D-glyceraldehyde belongs to the D-series. This is true of the acid resulting from oxidation of the aldehydic function; the substance is levorotatory and is therefore named D-(−)-glyceric acid. If the CHO group of glyceral-



dehyde is oxidized and the CH_2OH group is reduced, the resulting substance is lactic acid. Experimental correlation has established that levorotatory lactic acid, or *l*-lactic acid or (−)-lactic acid, corresponds in configuration to the reference standard and therefore is D-(−)-lactic acid. In the projection formula, hydroxyl is thus to the right and hydrogen to the left; this formula corresponds to the models shown at the right-hand side in paragraph 15.13 and in the corresponding tetrahedral diagrams.

15.17 Fischer's decision to call the series of natural (+)-glyceraldehyde the D-series was purely arbitrary. It was not until some sixty years later that special techniques of X-ray analysis were developed by which it became possible to determine whether compounds of Fischer's D-series actually have the configurations assigned or the opposite configurations. The results showed Fischer's choice to have been correct.

Absolute configuration

15.18 **Compounds with Two Dissimilar Asymmetric Carbon Atoms.** — Either addition of a symmetrical reagent to an unsymmetrical alkene or the reverse can give rise to substances having two asymmetric carbon atoms, for example:

$$CH_3CH_2CH{=}CHCH_3 \xrightarrow{[O],\,H_2O} CH_3CH_2\overset{*}{C}H(OH)-\overset{*}{C}H(OH)CH_3$$

$$HOOCCH{=}CHCOOH \xrightarrow{HOCl} HOOC\overset{*}{C}H(OH)-\overset{*}{C}H(Cl)COOH$$

$$C_6H_5CH{=}CHCH_3 \xrightarrow{Cl_2} C_6H_5\overset{*}{C}H(Cl)-\overset{*}{C}H(Cl)CH_3$$

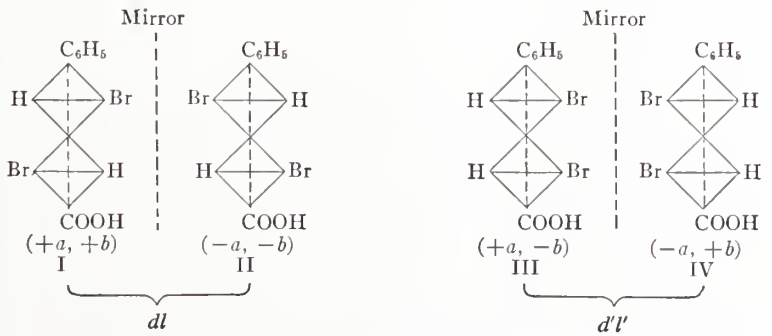
In each example the two asymmetric centers are dissimilar, and each therefore can contribute to a certain different extent to the rotatory power of the molecule as a whole in either a *dextro* or *levo* sense. If the contribution of one center of asymmetry is designated as $\pm a$ and the other as $\pm b$, then the possible combinations are:

$+a$ $+b$	$-a$ $-b$
dl-Form	

$+a$ $-b$	$-a$ $+b$
d'l'-Form	

Four optically active isomers

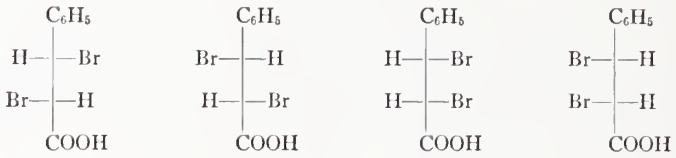
Theory therefore predicts four possible isomers, grouped in two pairs of enantiomeric modifications, or *dl*-mixtures, and this prediction has been verified. For example, two substances corresponding to the formula $C_6H_5\overset{*}{C}HBr\overset{*}{C}HBrCOOH$ are known; both are optically inactive but distinguished from each other by a difference in melting point, and both have been shown to constitute racemic mixtures. One, cinnamic acid dibromide, m.p. 201°, has been resolved into the active components of specific rotations +67.5° and −68.3°, and the other, allocinnamic acid dibromide, m.p. 90°, is also resolvable. Space formulas can be written for the four isomers, but since the configurations relative to glyceraldehyde are not known, a given formula cannot be assigned to a particular isomer. A first formula is constructed by joining two tetrahedrons together and affixing appropriate groups to the free corners in an arbitrary manner, for example, as in I. This arbitrary formula can be taken as representing a *d*-acid, in which the



Four diastereoisomers

upper half of the molecule is a $+a$ part and the lower half a $+b$ part. Formula II, representing the enantiomer of I, is constructed by visualizing the image of I in a mirror, and the upper and lower halves are, by definition, $-a$ and $-b$ parts. Formula III is made up of the upper half of I ($+a$) and the lower half of II ($-b$), and IV is its mirror image. Projection formulas utilizing the simplification that the asymmetric carbons are represented merely as the intersections of the lines connecting substituents are as follows:

Projection formulas



15.19 The two racemates are appropriately designated as *dl*- and *d'l'*-forms, and it is understandable that they should differ in melting point and other physical properties and indeed even in the rates at which they undergo reactions. The *d*-acid I is composed of two different asymmetric molecular halves ($+a$, $+b$), and the combination is neither duplicated nor mirrored in either the *d'*-acid III ($+a$, $-b$) or the *l'*-acid IV ($-a$, $+b$). Stereoisomers that, like the *d*-, *d'*-, and *l'*-acids, are not identical and yet are not mirror images, are defined as **diastereoisomers** (Gr. *dia*, apart). The *l*-acid II is the enantiomer of I, but is a diastereoisomer of III and IV.

15.20 **Compounds with Several Dissimilar Asymmetric Carbon Atoms.** — If three centers of asymmetry present in a given molecule can contribute in either a positive or negative sense to the extent of *a*, *b*, and *c* to the rotatory power of the molecule as a whole, then the possible combinations are:

$+a$ $-a$	$-a$ $+a$	$+a$ $-a$	$+a$ $-a$
$+b$ $-b$	$+b$ $-b$	$-b$ $+b$	$+b$ $-b$
$+c$ $-c$	$+c$ $-c$	$+c$ $-c$	$-c$ $+c$
dl	*d'l'*	*d''l''*	*d'''l'''*

Eight different optically active forms are possible, falling into four pairs of mirror-image isomers. A general relationship by which the number of isomers can be calculated is: number of optically active forms = 2^n (where n is the number of dissimilar asymmetric carbon atoms). When n = 4 the number of optically active forms possible is sixteen, and indeed an instance is known in the sugar series in which all sixteen isomers predicted by the van't Hoff-Le Bel theory are known.

Calculation of number of isomers

15.21 **Tartaric Acids.** — The tartaric acid series is the classical example of compounds possessing two similar asymmetric carbon atoms.

Pasteur had established that the inactive racemic acid can be resolved into *d*- and *l*-forms and is in fact *dl*-tartaric acid, and he had discovered another inactive isomer, mesotartaric acid. This isomer, typical of other substances which are therefore described generally as *meso* modifications, is produced along with the *dl*-acid by heating *d*-tartaric acid with water at 165° and can be isolated from the mixture in the form of the sparingly soluble acid potassium salt. The existence of two active and two inactive tartaric acids is readily explained. Since the rotatory contribution of each of two similar centers of asymmetry can be represented as $\pm a$, the following forms are predicted:

*CH(OH)COOH
|
*CH(OH)COOH

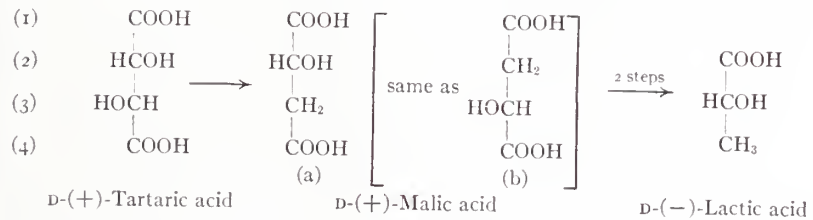
$$\underbrace{\begin{matrix} +a & -a \\ +a & -a \end{matrix}}_{dl\text{-Form}} \qquad \underbrace{\begin{matrix} +a \\ -a \end{matrix}}_{meso\ \text{Form}}$$

The combination of equal parts of the *d*- and the *l*-acid constitutes one inactive form, and the second or *meso* form is inactive because the molecule has a plane of symmetry. Mesotartaric acid is sometimes called an internally compensated inactive form, since there exists within each molecule a balancing of the right- and left-handed tendencies; *dl*-tartaric acid is inactive by virtue of compensation of an external nature: the presence of like numbers of two kinds of molecules.

Mesotartaric acid

Natural dextrorotatory tartaric acid, or (+)-tartaric acid, can be reduced to a substance identified as D-(+)-malic acid because it has

15.22

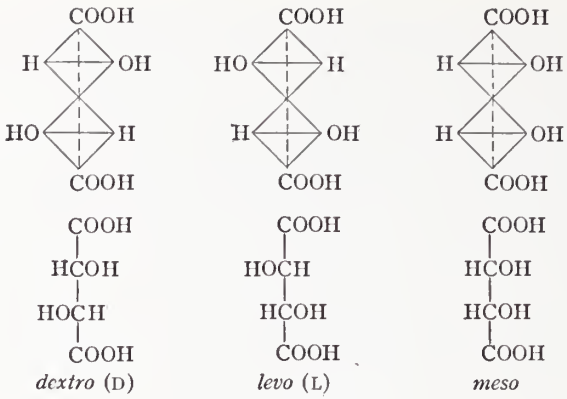


D-(+)-Tartaric acid — D-(+)-Malic acid — D-(−)-Lactic acid

d-tartaric corresponds to D-glyceraldehyde

been degraded in a series of steps to the reference substance D-(−)-lactic acid. It is immaterial whether reduction occurs at position 3 to give (a), or at position 2 to give (b), for when formula (b) is inverted it is seen to be identical with (a). Thus both asymmetric centers of natural tartaric acid have the D-configuration, and the substance is fully described as D-(+)-tartaric acid. The complete series of tartaric acids is represented on p. 258 in tetrahedral formulas and projections. The two asymmetric carbon atoms of *d*-tartaric acid make equal dextrorotatory contributions, and, as the formulas are written, the arrangement of the groups COOH, OH, and H (listed in order of decreasing size) is clockwise, or right-handed, in both the upper and lower centers. In the case of *l*-tartaric acid the arrangement is

Tetrahedral and projection formulas



Tartaric acids

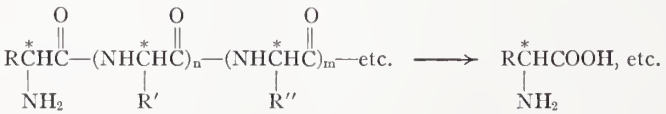
counterclockwise throughout, and in the *meso* acid the upper and lower centers are right- and left-handed, respectively.

15.23 **Enzymatic Resolution of *dl*-Mixtures.** — The resolution of racemic acid into *d*- and *l*-tartaric acid achieved in the classical experiment of Pasteur by crystallization and mechanical separation is an example of a method which is applicable only in very rare instances. However, Pasteur discovered two other more practical methods of resolution. While on a visit to the wine-making region of Bavaria, he acquired from an apothecary an old bottle of racemic acid on which a green mold had appeared. On returning to his laboratory he examined the remaining acid and found it to be levorotatory. The green mold was identified as the microorganism *Penicillium glaucum;* it is the mold found on aging cheese. When the microbes grow in a dilute aqueous solution containing racemic acid and nutrient salts, the originally optically inactive solution slowly becomes levorotatory because the microorganism preferentially assimilates natural *d*-tartaric acid.

Preferential action of a microorganism

15.24 Many instances are known of the preferential utilization of one of two enantiomers by microorganisms, and the action has been found due to enzymes necessary to growth. Enzymes, catalysts of biological reactions, are proteins, and like all proteins are made up of α-amino acids condensed together to form long chains. Proteins on hydrolysis

Due to enzymes present

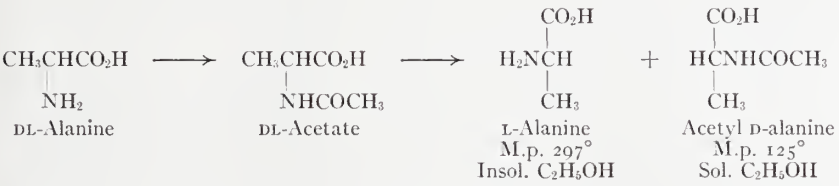


yield mixtures of the component acids. Most of the natural α-amino acids are optically active, and hence the proteinoid enzyme is optically active. Hence the preferential attack of a natural, optically active enzyme on the natural component of a *dl*-mixture is understandable.

15.25 The enzymatic method for many years was used mainly to de-

termine whether or not an optically inactive substance is resolvable. Thus mesotartaric acid develops no optical activity when acted on by *Penicillium glaucum*. Preparative use of the method ordinarily is limited by the fact that the more interesting natural enantiomer is the one sacrificed. In 1948, however, Jesse P. Greenstein of the National Cancer Institute at Bethesda developed a practical method for enzymatic resolution of the DL-forms of α-amino acids derived from proteins. Synthetic DL-alanine, for example, is acetylated, and the DL-acetate is treated with a solution containing an enzyme capable of effecting deacetylation. The solution is easily prepared from fresh

Resolution of amino acids



pork kidneys. Slices are agitated with water in a Waring blender and the homogenate centrifuged. The clear supernatant liquid containing enzyme is decanted into a bag made from cellophane sausage casing, which is then soaked in running water overnight to remove soluble nonproteinoid kidney components by dialysis, and the residual enzyme solution after a second centrifugation is ready for use. The action on the DL-acetate is complete in about four hours. The enzyme acts preferentially on the natural acetate and the result is a mixture of natural L-alanine and acetyl D-alanine. The mixture is easily separated because free alanine is insoluble in ethanol and the acetyl derivative is soluble.

General Method of Resolution. — After Pasteur had isolated unnatural *l*-tartaric acid for the first time, he prepared numerous salts of the new acid with inorganic and organic acids and compared them with the corresponding *d*-tartrates. The salts of *d*- and *l*-tartaric acid with metals, ammonia, and aniline were identical in solubility and other physical properties; but Pasteur observed that with salts derived from asymmetric, optically active natural bases such as quinine or strychnine "all is changed in an instant. The solubility is no longer the same and the properties all differ as much as in the case of the most distantly related isomers." The reason is apparent from consideration of an example. If a *dl*-acid is neutralized with a dextrorotatory (*d'*) base, one of the two salts produced is composed of two right-handed parts (*dd'*), and the other is made up of right-

15.26

Salt of dl-acid with optically active base



and left-handed components (*ld'*). The two salts obviously differ in rotatory power and are in fact diastereoisomers. If the acidic and basic components are strongly rotatory, the *dd'*-salt probably will be dextrorotatory; the *ld'*-salt is composed of oppositely acting but unbalanced parts and may show either positive or negative rotation. In any case, the two salts have different rotatory values, different solubilities, and different melting points; they therefore are separable by fractional crystallization, and the course of separation can be followed by determination of appropriate physical constants. Once one salt has been secured pure, it can be treated with sodium hydroxide, the resolving *d'*-base recovered, and the optically active acid liberated by acidification of the alkaline solution.

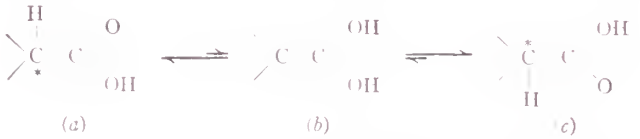
15.27 *Variations in the method*

The method is equally applicable to resolution of a synthetic *dl*-amine with an optically active acid. Sometimes resolution of a neutral compound is accomplished most advantageously by conversion into a derivative capable of salt formation. An often efficient modification in the procedure of resolution consists in treating a *dl*-base with half the amount of a resolving organic acid required for neutralization, together with a further half equivalent of hydrochloric acid. Equilibrium is set up among the two pairs of salts, but those derived from the organic acid are distinctly less soluble than the hydrochlorides. Thus the less soluble of the two diastereoisomeric organic salts tends to crystallize, and the solution contains chiefly the hydrochloric acid salt of the enantiomeric amine.

15.28 **Racemization.** — Conversion of half a given quantity of an optically active compound into the enantiomer is defined as racemization. The experiment by Pasteur in which *d*-tartaric acid was converted by the action of water at 165° into a mixture of the *meso* and *dl*-acids involved racemization of a part of the material. The racemic (*dl*) acid occurring as a by-product of the production of *d*-tartaric acid in the wine industry probably arises by partial racemization of the *d*-acid during processing.

15.29 Racemization occurs especially readily with compounds having a carbonyl group adjacent to an asymmetric carbon carrying a hydrogen atom, for example tartaric acid, lactic acid, and glyceraldehyde. Where the specific grouping indicated is lacking, racemization usually proceeds with difficulty, if at all. Thus, in contrast with mandelic acid, $C_6H_5CHOHCOOH$, atrolactic acid, $C_6H_5C(CH_3)OHCOOH$, does not undergo racemization. These facts suggest that the α-hydrogen atom plays a part and that enolization is involved. If the activated α-hydrogen atom in (*a*) migrates to oxygen in an equilibrium process to give an enol (*b*), the center of asymmetry is destroyed temporarily by production of a double bond, and when the hydrogen migrates

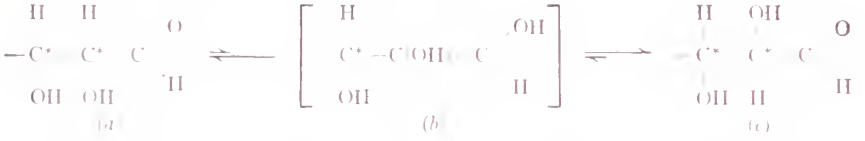
back to the carbon atom, the process can involve opening of either of the two linkages of the symmetrical double bond, and hence can



Ready racemization through an enol

afford either the original configuration (*a*) or the opposite configuration (*c*); the chances being equal, a mixture of equal parts of (*a*) and (*c*) results. Since all the transformations are reversible, formation of only a minute amount of the enol would result in eventual racemization of the entire material. The interpretation is strengthened by the fact that racemization is promoted by acids and bases, reagents which catalyze enolization.

Epimerization. In a compound having more than one asymmetric carbon atom, selective racemization of an asymmetric center adjacent to a carbonyl group and possessing a hydrogen atom available for enolization is possible, for example: 15.30



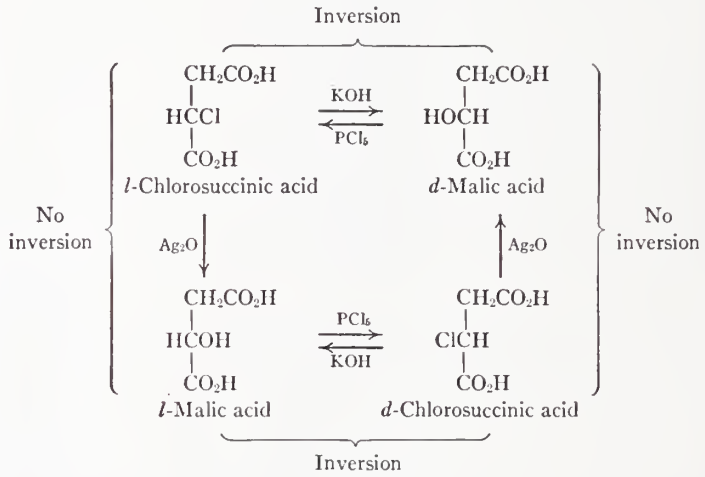
Selective inversion at one center

The result is transformation of the original substance (*a*) partially into the isomer (*c*), which has been selectively inverted at a single asymmetric center and is described as an epimer of the first substance. The term epimer designates a pair of diastereoisomers that correspond in configuration of all but one of several centers of asymmetry and that have the opposite configuration at this one center. Epimerization is not complete but proceeds to a point of equilibrium between epimers (*a*) and (*c*). It is not a 50:50 equilibrium, as in the racemization of a compound with just one asymmetric center, and the position of equilibrium varies from case to case. The participants (*a*) and (*c*) are diastereoisomers of different rotation, different stability, and different energy of formation.

Walden Inversion. The discoverer of this interesting phenomenon (1896), Paul Walden, was born in Russia and held professorships in both Russia and Germany. He found that when one substituent directly linked to an asymmetric carbon atom is replaced by another, the original center of asymmetry sometimes, but not always, becomes inverted in the process, with the result that its configuration in the product is the opposite of that in the starting material. The phe- 15.31

nomenon is distinct from that of racemization, for one optically active compound is converted into another, rather than into a *dl*-mixture, and it is not a matter of change in the direction of rotation, which may or may not follow and is coincidental, but rather a question of change in the absolute configuration. Examples are the interconversions of optically active chlorosuccinic and malic acids shown in the chart with projection formulas giving configurations relative to the configuration of glyceraldehyde (*l*-malic acid = D-series). *l*-Chlorosuccinic acid on hydrolysis with potassium hydroxide affords a hydroxy acid of opposite configuration. That the dextrorotatory character

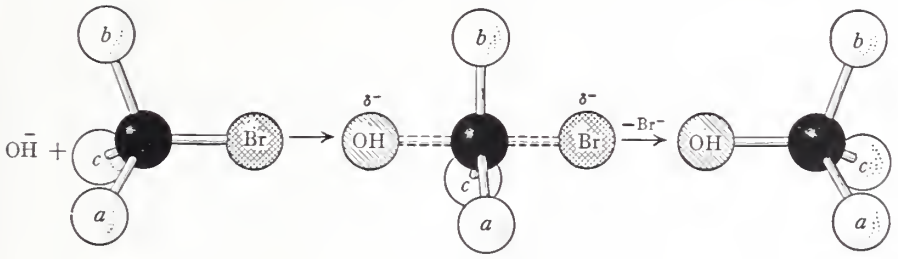
Example of inversion and retention



of the product is fortuitous can be appreciated from the fact that the malic acids show but feeble rotatory power, with considerable dependence on the concentration of the solutions. The evidence indicates, however, that a Walden inversion occurs in this reaction and in the reverse change brought about by phosphorus pentachloride. On the other hand, the chlorosuccinic acids are hydrolyzed by silver oxide without inversion.

15.32 The Walden inversion presented a perplexing problem in interpretation which was only solved with the development of modern concepts of reaction mechanisms. Whether a given reaction proceeds with inversion or with retention of configuration is now recognized as dependent upon the reagent, the conditions of the experiment, and the specific characteristics of the substance undergoing reaction. The combination of these factors determines the particular mechanism by which the reaction proceeds. If the hydrolysis of an alkyl bromide (I) is bimolecular, the anion attacks the molecule from the rear (S_N2 mechanism; see 11.6). This backside attack affords a transition state in which the hydroxide ion has given up part of its charge to bromine

and in which neither group is fully joined to carbon or fully separated. In the transition state the fractionally charged (δ^-) OH and Br lie in a line and the groups *a*, *b*, and *c* lie in a plane perpendicular to this line. Bromine is then expelled as the anion from one side, with synchronous attachment of hydroxyl to the other side by a covalent link.



I Transition state II

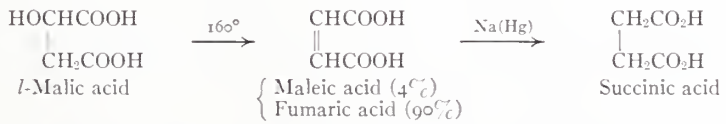
S_N2 reaction with inversion

The result is the alcohol II, of configuration opposite to that of I. The process of inversion is thus like the turning of an umbrella inside out in the wind.

Geometrical Isomerism. — The first experimental demonstration of the existence of a pair of geometrical isomers as postulated by van't Hoff was in a research by Wislicenus in 1887 on two acids that result from pyrolysis of malic acid: maleic acid (m.p. 130°) and fumaric acid (m.p. 287°). That the difference between them is associated

15.33

Review Paragraph 2.21



Maleic and fumaric acid

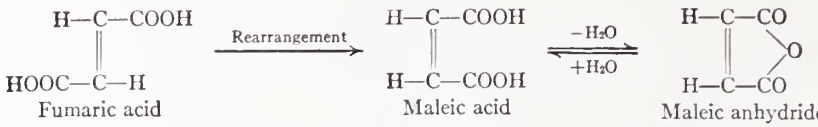
with the double bond is established by its disappearance on hydrogenation; both isomers yield succinic acid. The formulas show that the *cis*, but not the *trans*, isomer should form a cyclic anhydride



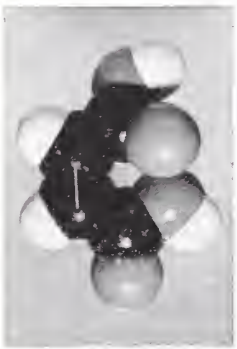
comparable to succinic anhydride. Maleic acid indeed forms an anhydride (m.p. 57°), but, since fumaric acid yields the identical anhydride under more drastic conditions, a molecular rearrangement must occur in one of the two reactions and the evidence is inconclusive. However, the anhydride can be hydrolyzed with cold water, that is, under conditions where rearrangement is excluded, and maleic acid is the sole product. Therefore maleic acid has the *cis*-configuration, and the product of dehydration is maleic anhydride. Fumaric acid is the *trans*-isomer, and when heated strongly or treated with chemical

Evidence of configuration

dehydrating agents under forcing conditions, rearranges into maleic acid, which then yields the anhydride:



That the more symmetrical *trans*-configuration is more stable than the *cis* is shown by the higher melting point of fumaric acid (Table 15.33), the greater density (closer packing), the lesser solubility, and by the fact that when maleic acid is heated in a sealed tube to prevent escape of water it yields fumaric acid as the chief product (trace of *dl*-malic acid). The heats of combustion show that maleic acid has



Maleic acid

TABLE 15.33

PHYSICAL PROPERTIES OF MALEIC AND FUMARIC ACIDS

	Maleic acid *cis*	Fumaric acid *trans*
Melting point	130°	287°
Solubility in water, g. per 100 ml. at 25°	78.8	0.7
Density	1.590	1.635
Heat of combustion, kg.-cal. per mole	327	320
pK_{a_1}	1.9	3.0
pK_{a_2}	6.5	4.5



Fumaric acid

an energy content 7 kg.-cal. higher than fumaric acid and therefore has greater tendency to undergo change. That the *cis*-isomer is the more strongly acidic, as judged by comparison of the constants for the first dissociation, pK_{a_1}, means that the ionizing tendency of one carboxyl group is enhanced by the second unsaturated group in a near-by position. The greater spread between the first and second dissociation constants observed with maleic acid is also understandable. Once a proton has separated from the *cis* dibasic acid, the negatively charged group exerts an attractive force on the second hydrogen atom in the neighboring position and opposes its liberation as a proton.

15.34 The energy-richer *cis*-isomer is convertible into fumaric acid at room temperature under the catalytic influence of hydrochloric or hydrobromic acid. The halogens as well as the halogen acids are effective catalysts for the rearrangement; for example, diethyl maleate is transformed rapidly into the ester of fumaric acid by a trace of iodine. The transformations represent the reversion of a labile isomer to a more stable form under the driving force derived from the higher energy content. The reverse change is brought about by irradiation of an aqueous solution of fumaric acid with ultraviolet light at 45–50°;

within a few hours, equilibrium is reached corresponding to isomerization of 75% of the material. Here the *trans*-isomer acquires radiant energy by absorption, and the energy level is built up to that of the *cis*-isomer.

cis ⇌ trans

SUMMARY

History

Polarization of light (Malus, 1808). Nicol prism (transmits a single ray of polarized light). Rotation of plane polarized light by quartz crystals that are hemihedral (having half the faces required for symmetry). Discovery that certain organic compounds exhibit optical activity in solution (Biot, 1815). Principle of the polarimeter. Specific rotation, $[\alpha]$. Dextrorotation (+), levorotation (−).

Discoveries of Pasteur. Resolution of racemic acid into *d*- and *l*-tartaric acids (1848) by slow crystallization of the sodium ammonium salt at a temperature fortuitously below a critical transition point. Recognition that the tartaric acids must possess molecular asymmetry. Discovery of a fourth, optically inactive, isomer (mesotartaric acid).

The lactic acids: *d*-acid of muscle tissue, *l*-acid from bacterial fermentation of milk sugar. Wislicenus' proof (1863–73) of identity of structure; synthesis of *dl*-acid; conclusion that the acids differ in the arrangement of atoms in space.

Theory of van't Hoff and Le Bel (1874). Concept of the tetrahedral nature of the carbon atom. Asymmetry attending attachment to carbon of four different atoms or groups. Correlation of optical activity with the presence of an asymmetric carbon atom.

Optical Isomerism

Compounds with one asymmetric carbon atom. Models of *d*- and *l*-lactic acid. Inference that *d*- and *l*-forms must be identical in all chemical and physical properties except effect on plane polarized light. Mirror-image isomers called enantiomers. Synthesis of compounds having an asymmetric carbon atom offers equal probability of producing the *d*- or *l*-form; hence a *dl*-mixture invariably results.

Correlations and conventions. Derivatives of a *d*-acid may differ in magnitude and even sign of rotation and still belong to the same stereochemical series. Conventional reference standard: dextrorotatory glyceraldehyde, $HOCH_2CH(OH)CHO$, defined as D-(+)-glyceraldehyde. E. Fischer's formulas; method of orienting model. Other members of the D-series: D-(−)-glyceric acid, D-(−)-lactic acid, D-(−)-malic acid. Fischer's arbitrary choice later shown to have been the correct one.

Compounds with dissimilar asymmetric carbon atoms. Possible variations when two asymmetric carbon atoms are present: $+a+b$, $-a-b$, $+a-b$, $-a+b$. Tetrahedral formulas and planar projections for four isomeric acids

$$C_6H_5\overset{*}{C}HBr\overset{*}{C}HBrCO_2H.$$

Definition of diastereoisomers: nonidentical isomers of the same structure that are not mirror-image isomers (enantiomers). Number of isomers = 2^n (n = number of dissimilar asymmetric carbon atoms).

Tartaric acids: *d*-, *l*-, *dl*- (racemic), and *meso*-. Variations for two similar asymmetric carbon atoms: $+a+a$, $-a-a$, $+a-a$ (*meso*). Tetrahedral and projection formulas.

Enzymatic resolution of *dl*-mixtures. Pasteur: the microorganism of a mold assimilates and destroys natural *d*-tartaric acid faster than the unnatural enantiomer. Early use: to determine if an inactive compound is *dl* (resolvable) or *meso* (nonresolvable). Action due to an optically active enzyme, a protein composed of α-amino acids condensed to a long chain. Greenstein's method of resolving DL-amino acids, e.g. DL-alanine; acetylate and let an enzyme preparation from pork kidney act on the DL-acetate; it selectively deacetylates the natural L-acetate, and L-alanine is easily separated from the D-acetate.

Resolution of a *dl*-acid by formation of salts with a *d'*-base: *dd'*-salt and *ld'*-salt are diastereoisomers of different rotation and different solubility, separable by fractional crystallization. Resolution of a *dl*-amine with an optically active acid.

Racemization: conversion of *d*- or *l*-form to *dl*-form. Occurs readily where asymmetric carbon carries a hydrogen atom and is adjacent to a carbonyl group. Mechanism through enol. Epimerization: partial transformation to an isomer that is inverted at one of two or more centers of asymmetry (epimer); realizable whenever enoliza-

tion involving a single center is possible, i.e. in —$\overset{*}{C}$HOH$\overset{*}{C}$HOHCOOH. Position of equilibrium varies from compound to compound.

Walden inversion. Replacement of a group attached to an asymmetric carbon atom often gives a product of the opposite stereochemical series. Example: D-$R_1R_2R_3CCl \longrightarrow$ L-$R_1R_2R_3COH$. Explanation: bimolecular reaction involving backside attack, transition state, expulsion of group as ion (umbrella turned inside out).

Geometrical Isomerism

van't Hoff's prediction of *cis-trans* forms of unsymmetrically substituted alkenes confirmed.

Maleic and fumaric acid by dehydration of malic acid (fumaric acid the chief product). Reduction of both isomers to succinic acid, which forms a cyclic anhydride. Maleic acid forms an anhydride easily; fumaric gives the same anhydride with greater difficulty, but rearrangements obscure relationships. Reversion of the anhydride to maleic acid on low-temperature hydrolysis proves maleic acid to have *cis*-configuration. Fumaric acid (*trans*) is the more symmetrical and has the higher melting point, lower solubility, greater density. Higher heat of combustion of maleic acid (*cis*) indicates greater energy content, greater lability. Energy-rich *cis*-form rearranges to stable *trans*-form on catalysis by X_2 or HX. Reverse transformation, *trans* $\longrightarrow$ *cis* accomplished by irradiation (absorption of energy).

PROBLEMS

1. An asymmetric center is produced in the reaction:

$$CH_3CH_2CO_2H + Br_2 \longrightarrow CH_3CHBrCO_2H + HBr.$$

Explain why the product is optically inactive.

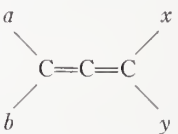
2. Write projection formulas for all the stereoisomeric forms of $HOOCCH(CH_3)CHBrCOOH$. Which are enantiomers and which diastereoisomers?
3. How many optically active forms corresponding to the following formulas are possible?

(*a*) $CH_3CH_2CH(OH)CHClCH_3$
(*b*) $(CH_3)_2CHCH_2CH(CH_3)COOH$
(*c*) $C_6H_5CHBrCH_2CH(OH)CH_2CH(NH_2)COOH$
(*d*) $CH_2(OH)CH(OH)CH(OH)CH(OH)CH(OH)CHO$

4. An acid of the formula $C_5H_{10}O_2$ is optically active. What is its structure?
5. A derivative of one of the tartaric acids is optically active but gives optically inactive products when esterified with diazomethane or when hydrolyzed. What is it?
6. Give the number and nature of the possible stereoisomers, if any, corresponding to each of the following formulas:

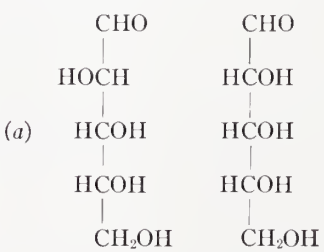
(*a*) $(CH_3)_2CHCH(NH_2)CH_2CH(CH_3)_2$
(*b*) $CH_3CH_2C(CH_3)=C(CH_3)_2$
(*c*) $C_6H_5CH=CHCOC_6H_5$
(*d*) $CH_2=CHCH_2CH(NH_2)COOH$
(*e*) $C_6H_5CHBrCHBrCOC_6H_5$
(*f*) $(C_6H_5)_2C=CHCH_2CH_2CH=C(C_6H_5)_2$
(*g*) $CH_3CH(OH)CH(OH)CH_3$
(*h*) $HOCH_2CH(OH)CH(OH)CH(OH)COOH$

7. When a dextrorotatory isomer of the formula $HOCH_2CH(OH)CH(OH)CHO$ is boiled with dilute hydrochloric acid the rotatory power increases for a time and then becomes constant. What is the nature of the change?
8. Certain substances of the type $R_1R_2R_3R_4N^+X^-$ have been resolved into optically active components. What inference can be drawn regarding the spatial character of the nitrogen atom?
9. van't Hoff made a prediction, verified some sixty years later, concerning the stereochemistry of allenes of the following type:

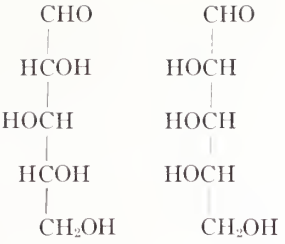


What phenomenon would you anticipate in such a structure?

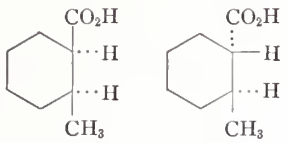
10. Which of the following pairs of diastereoisomers are epimers, and which epimer pairs offer prospect for easy interconversion?



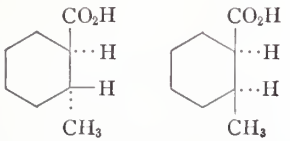
(*b*)



(*c*)

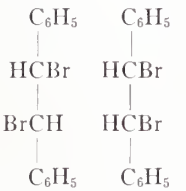


(*d*)

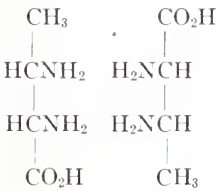


11. Identify the following isomer pairs. (1) Are they enantiomers, epimers, diastereoisomers, geometrical isomers, structural isomers, or identical? (2) Which members are optically active?

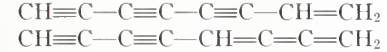
(*a*)



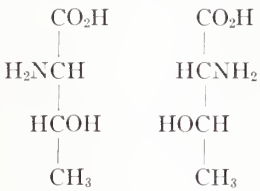
(*b*)



(*c*)

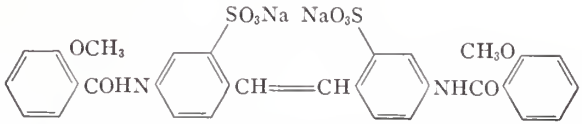


(*d*)



(*e*) *l*-Quinine *d*-tartrate *l*-Quinine *l*-tartrate

12. The compound formulated below, which exhibits brilliant blue fluorescence in dilute aqueous solution and which has affinity for cotton fabric, is employed, in its most stable steric form, as a brightening agent, or colorless dye added to soap to increase whiteness of washed goods. What change would you expect to occur when the washed material is exposed to sunlight?



13. Mescal, a preparation from the tops of the small cactus *Lophophora williamsii*, is used as a stimulant and antispasmodic, especially among Mexican Indians, who also employ it as a mild intoxicant in various ceremonials. The active principle, mescaline, was isolated in 1896 by A. Heffter (Leipzig) from material supplied by Parke, Davis and Co. Mescaline (A), $C_{11}H_{17}O_3N$, melts at 36°, is optically inactive, sparingly soluble in water or in sodium hydroxide solution, but soluble in dilute hydrochloric acid. Zerewitinoff determination shows the presence of one active hydrogen, and reaction with acetic anhydride in pyridine gives a neutral derivative (B), $C_{13}H_{19}O_4N$. When A is shaken with benzenesulfonyl chloride and aqueous alkali the substance gradually dissolves, and acidification of the solution gives a crystalline precipitate (C), $C_{17}H_{21}O_5NS$. Mescaline on reaction with excess methyl iodide, followed by treatment of the product with moist silver oxide, gives a product D, $C_{14}H_{23}O_4N$, which when heated decomposes to trimethylamine and a neutral compound E, $C_{11}H_{14}O_3$. Oxidation of E with OsO_4, followed by HIO_4 gives formaldehyde and 3,4,5-trimethoxybenzaldehyde. Deduce the structure of mescaline.

CHAPTER 16

CARBOHYDRATES

16.1 Carbohydrates, including the sugars, are among the most abundant constituents of plants and animals, in which they serve many useful functions. They are a source of energy; they form supporting tissues of plants and of some animals in the same way that proteins are used by most animals. The name is derived from the fact that many sugars have the empirical formula $C_nH_{2n}O_n$, or $C_n(H_2O)_n$, and hence the French applied the name "hydrate de carbone" or carbohydrate, and the name has been retained even though it is not descriptive. They are classified systematically as monosaccharides, di-, tri-, and tetrasaccharides, and polysaccharides. Practically all natural monosaccharides contain five or six carbon atoms, and are known as pentoses and hexoses, respectively. They are colorless, crystalline substances, usually with a sweet taste. Disaccharides, which are condensation products of two hexose or pentose units, resemble monosaccharides in taste, color, and solubility. Polysaccharides are tasteless, amorphous, insoluble substances of the type formula $(C_6H_{10}O_5)_n \cdot H_2O$ or $(C_5H_8O_4)_n \cdot H_2O$, in which n is known to be large. They are converted on hydrolysis into C_6- or C_5-sugars, as the simple disaccharides are. Cane sugar (sucrose) yields two C_6-sugars or hexoses, glucose and fructose. The disaccharide sucrose is dextrorotatory, but the mixture of hexoses resulting on hydrolysis is levorotatory and is known as invert sugar. Honey is largely invert sugar, since bees contain an enzyme (invertase) capable of hydrolyzing sucrose.

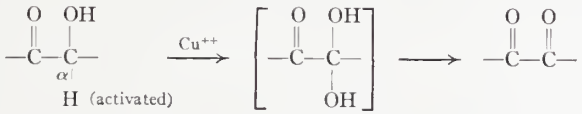
Classification

Inversion of sucrose

$$\underset{\substack{\text{Sucrose}\\ [\alpha]_D\ +66.5^\circ}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{\substack{\text{Glucose}\\ [\alpha]_D\ +52^\circ}}{C_6H_{12}O_6} + \underset{\substack{\text{Fructose}\\ [\alpha]_D\ -92^\circ}}{C_6H_{12}O_6}$$

16.2 The suffix *-ose* is a generic designation of a sugar. Glucose is an aldehydic sugar with six carbon atoms, or an aldohexose. Fructose is a ketonic hexose or ketohexose.

Structures of Glucose and Fructose. — Both glucose and fructose were recognized as carbonyl compounds by their ability to reduce Fehling's solution (complex cupric ion), a property characteristic of both aldehydes and α-hydroxy ketones: 16.3

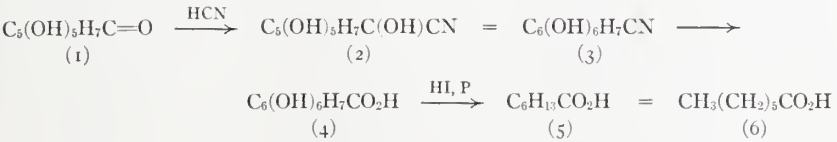


The reaction distinguishes between carbonyl-containing sugars that reduce Fehling's solution (reducing sugars) and those that contain no free or potential carbonyl group and are nonreducing (sucrose).

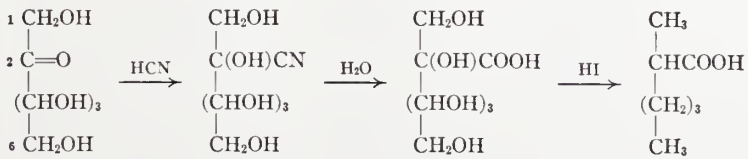
Reducing sugars

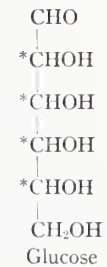
Both glucose and fructose react with acetic anhydride to give crystalline pentaacetates and therefore the six oxygen atoms in both substances are accounted for as five hydroxyl groups and one carbonyl group, and the formulas may be written $C_5(OH)_5H_7C{=}O$. The nature of the carbon skeleton of glucose and the position of the carbonyl group were established by Heinrich Kiliani (1886) on discovery that hexoses add hydrogen cyanide. The cyanohydrin (2) from glucose (1) can be represented as in (3) and the acid produced on hydrolysis as (4). Kiliani reduced the hydroxy acid (4) with hydriodic acid and 16.4

Location of carbonyl group



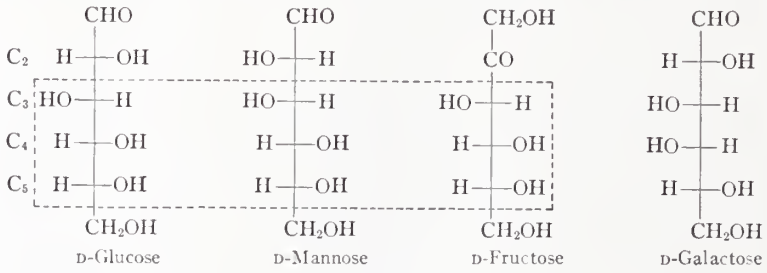
red phosphorus to replace the hydroxyl groups by hydrogen, and identified the reduction product (5) as *n*-heptylic acid (6). The extra carbon atom introduced on addition of HCN is thus found at the end of a six-carbon straight chain and the carbonyl group is at the end of this chain and is therefore aldehydic. Since a six-carbon aldehyde having five hydroxyl groups can have a stable structure only if just one of these groups is distributed on each of the available five carbon atoms, glucose is inferred to have the formula shown. Kiliani carried out a similar series of reactions with fructose; the final acid is methyl-*n*-butylacetic acid, from which Kiliani deduced that fructose is a pentahydroxy ketone with the carbonyl oxygen atom at the 2-position of the chain; it is a 2-ketohexose.





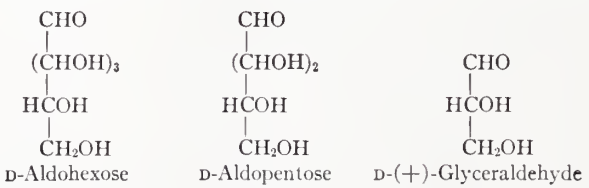
16.5 **Configurations.** — Glucose has four dissimilar asymmetric carbon atoms and is therefore one of sixteen possible optical isomers; fructose is one of eight possible 2-ketohexoses. Only two other aldohexoses, mannose and galactose, occur widely in nature, and fructose is the only common natural ketohexose. The synthesis of most of the remaining thirteen aldohexoses and seven 2-ketohexoses was accomplished by Emil Fischer in a brilliant series of investigations of 1891–96 that completely elucidated the configurations of all the known isomers, natural and synthetic. Fischer's representation of natural, dextrorotatory glucose is shown in the accompanying projection formula (convention for projection formulation, 15.15). Mannose is the

The natural hexoses



C_2-epimer of glucose, since it differs only in the configuration at C_2; in the projection formula the hydrogen at C_2 is to the right and hydroxyl to the left. Fructose corresponds in configuration at all three of its asymmetric centers to carbon atoms 3, 4, and 5 of glucose and of mannose. Galactose is the C_4-epimer of glucose. Position 5 is the only center at which all four natural hexoses correspond in configuration, and hence Fischer elected the configuration at C_5 as the distinguishing characteristic of a stereochemical series defined as that of natural glucose. He succeeded in relating glucose to D-tartaric acid, which had already been shown to belong to the same steric series as D-glyceraldehyde, represented in the conventional projection formula with hydroxyl written to the right and hydrogen to the left. The configuration of glucose at C_5 thus defines the D-series, and any sugar, whether it is aldehydic or ketonic and regardless of the number

D-Series



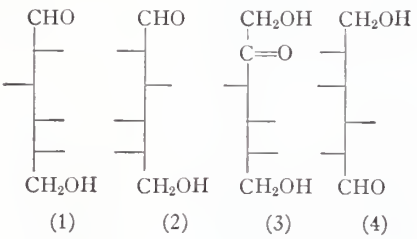
of carbon atoms and the sign of rotation, belongs to the D-series if it corresponds to D-glucose at the next to the last carbon atom. Natural fructose is a D-sugar even though it is levorotatory; for full description

it can be called D-(−)-fructose. The formulas selected for conventional representation of D-glyceraldehyde and of D-glucose were arbitrary but were later (1951) proved correct by X-ray crystallography.

16.6

A projection formula of an aldose is conveniently abbreviated by writing just the terminal groups and indicating a hydroxyl group to the right or left by a bar. D-Glucose is thus (1), and the enantiomer,

Convenient abbreviation



(1) (2) (3) (4)

L-glucose, is (2). D-Fructose can be represented as in (3). A formula can be turned in the plane of the paper until inverted without loss of identity; for example, (4) is as valid a representation of D-glucose as (1).

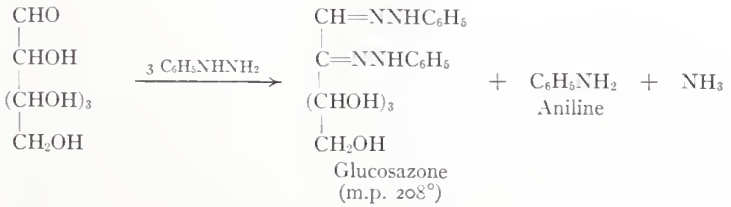
16.7

All sixteen aldohexoses are known, and of these only the three that occur naturally are fermented to ethanol and carbon dioxide by yeast enzymes: D-glucose, D-mannose, and (less rapidly) D-galactose. Natural D-fructose is fermentable. Yeasts are unable to ferment the corresponding enantiomers of the L-series.

16.8

Osazones. — Early progress in elucidation of sugar chemistry was handicapped by the difficulty in obtaining crystalline compounds, since sugars, especially when impure, tend to form sirups. One of the outstanding contributions of Fischer was introduction in 1884 of the use of phenylhydrazine, which was found to react with many carbonyl compounds to give sparingly soluble and beautifully crystalline derivatives. Fischer's dissertation for the doctorate under Baeyer at Strasbourg ten years earlier had described the discovery, preparation, and uses of phenylhydrazine. The reaction with sugars proceeded in an unexpected manner, since Fischer found that the products, which he called osazones (–ose + hydrazone), contained two phenylhydrazine residues rather than one.

Fischer's reagent useful for isolation

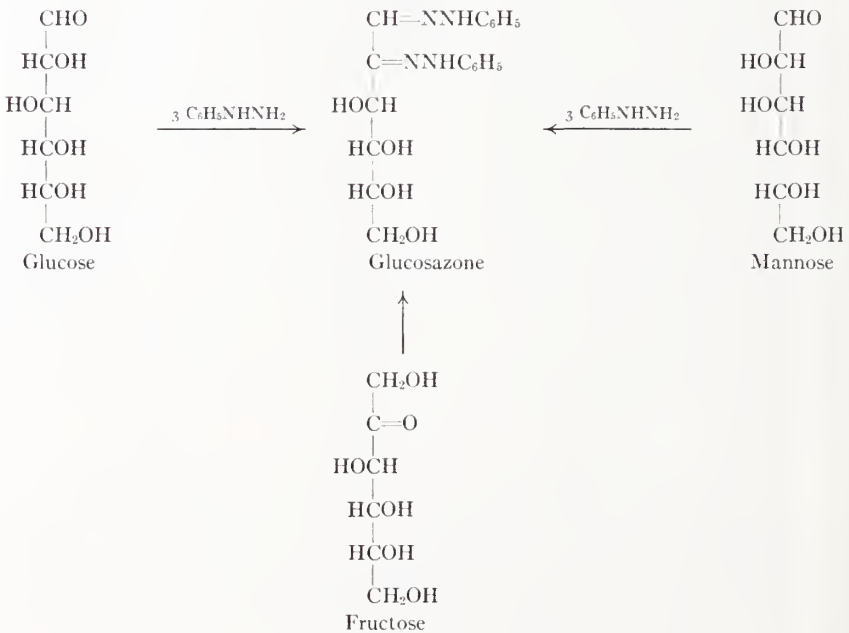




Emil Fischer, 1852–1919
Born Euskirchen, Germany; Ph.D. Strasbourg (Baeyer); universities of Erlangen, Würzburg, Berlin; Nobel Prize 1902

16.9 Osazones are bright yellow, crystalline compounds identifiable both from their temperatures of decomposition and from the crystalline forms. That the solubility in water is markedly less than that of the sugar is understandable, for introduction of two phenylhydrazine residues into a hexose increases the molecular weight by 64%, and the derivative contains one less hydroxyl group. Thus an osazone, which is produced easily by brief warming of a solution containing the reagent, usually will separate from a dilute solution of an impure sugar.

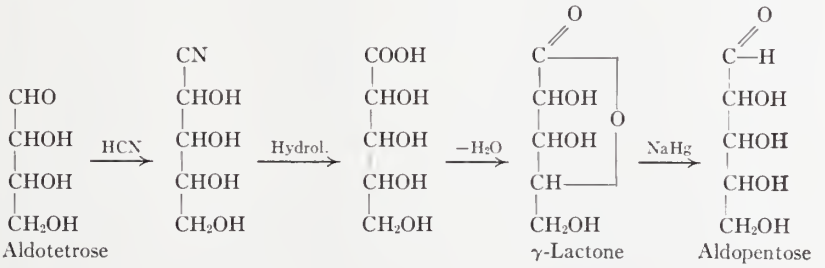
Correlation through a common osazone



Since osazone formation eliminates asymmetry at C_2 in an aldose, mannose gives the same osazone as glucose. The same substance, glucosazone, also results from reaction of phenylhydrazine with fructose. Thus osazone formation, like reduction of Fehling's solution, is a property characteristic of α-hydroxy ketones as well as of α-hydroxy aldehydes. Actually osazone formation was useful in establishing relationships between hexoses. Thus once mannose was established to be an aldohexose, formation from it of the same osazone that had been obtained from glucose identified mannose as the C_2-epimer of glucose. Formation of glucosazone from fructose showed this ketose to correspond to glucose in all its centers of asymmetry. Galactose is the C_4-epimer of glucose and therefore gives a different osazone. 16.10

Ketoses give osazones

Cyanohydrin Synthesis. — The reaction with hydrogen cyanide (Kiliani) is the first step in a method of synthesis of higher sugars from lower ones. The cyanohydrin from an aldotetrose on hydrolysis gives an acid with hydroxyls at the α-, β-, γ-, and δ-positions with respect to the carboxyl group. The presence in a molecule of both 16.11

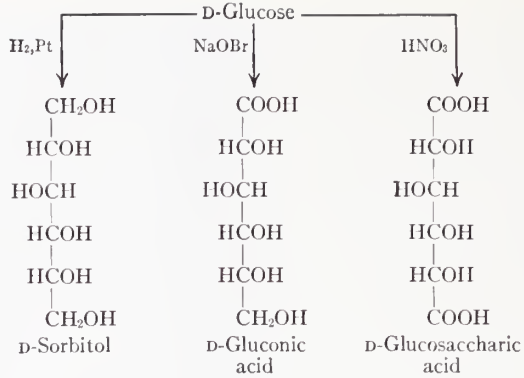


Aldotetrose → aldopentose

hydroxyl and carboxyl functions opens the possibility for formation of an internal ester, or lactone. A γ-lactone with a five-membered ring is considerably more stable than a β- or δ-lactone (α-lactones are nonexistent). The sugar acid thus yields exclusively the γ-lactone, and indeed is lactonized merely by warming an acidified aqueous solution. The γ-lactone is then reduced with sodium amalgam, a reaction which involves fission of the oxide link with restoration of the original γ-hydroxyl group and generation of an aldehyde group with formation of an aldopentose.

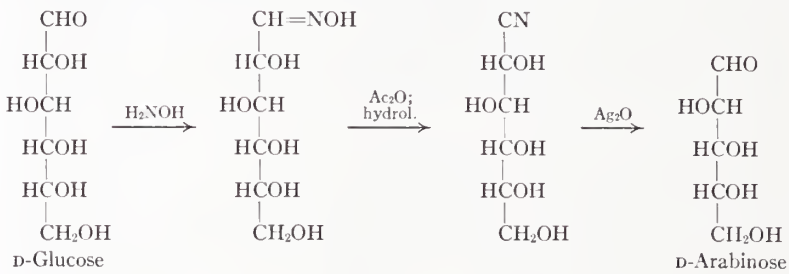
Formation and reduction of a γ-lactone

Oxidation and Reduction. — When glucose is reduced by catalytic hydrogenation or electrolytically, the reduction product is sorbitol. Oxidation with hypobromite attacks the aldehydic group and gives a monobasic acid, gluconic acid; nitric acid attacks both the aldehydic group and the primary alcoholic group to give the dibasic glucosaccharic acid. 16.12



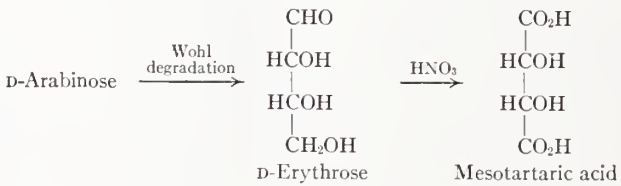
16.13 **Wohl Degradation.** — The correlation of aldohexoses with aldopentoses is facilitated by degradation of the former to the latter by a method introduced by Alfred Wohl (Germany, 1893). This involves formation of the oxime, dehydration to a cyanohydrin, and reversal

Reversal of cyanohydrin synthesis



of the usual cyanohydrin synthesis. The Wohl degradation eliminates the aldehydic C_1 atom and converts C_2 into a new aldehydic group. Glucose is thus transformed into the pentose arabinose. A second degradation applied to arabinose affords the tetrose erythrose, and

Correlation with a tartaric acid

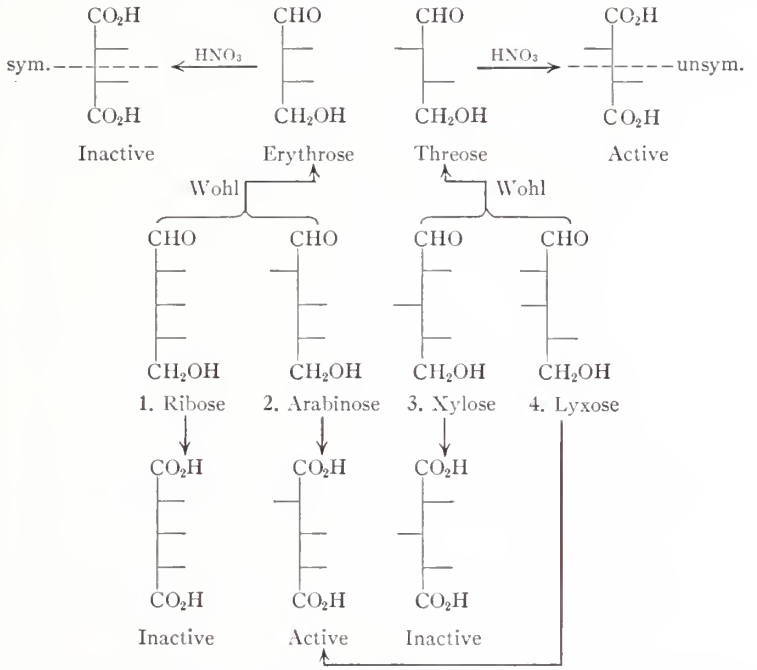


oxidation of the terminal groups of this substance with nitric acid gives mesotartaric acid. The overall process thus proves that carbon atoms 4 and 5 in glucose correspond in configuration to the two asymmetric centers of mesotartaric acid.

16.14 **Configurations of Tetroses and Pentoses.** — The configurations of the two D-tetroses, erythrose and threose, can be distinguished experimentally in a simple manner: nitric acid oxidation and examination of the resulting C_4-diacids for optical activity. The product from erythrose has a plane of symmetry and hence is optically in-

active (mesotartaric acid); that from threose is not symmetrical and is optically active (D-tartaric acid).

Two of the four D-pentoses, ribose and arabinose, are C_2-epimers related to erythrose in that they both yield this substance on Wohl 16.15



D-Pentoses, RAXL

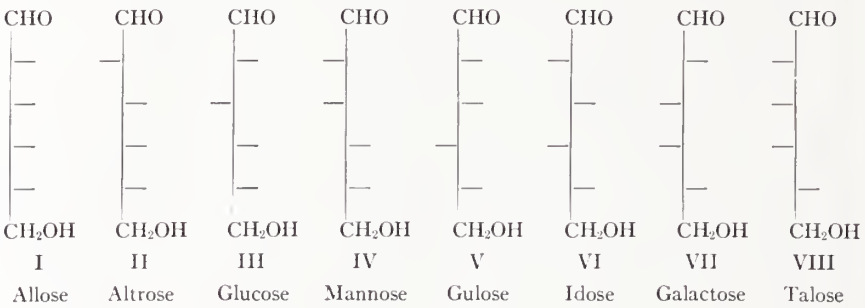
C_5-Diacids

degradation. Xylose and lyxose are related in the same way to threose. The C_5-diacids (saccharic acids) resulting on oxidation of the pentoses with nitric acid are characterized as follows: ribose gives an inactive acid and arabinose an active one; xylose gives a different inactive acid, while that from lyxose is active and if the formula is inverted this is seen to be identical with the acid from arabinose. If the configurations were unknown, they could be deduced as follows. Ribose can be assigned formula (1) because it is the only pentose which affords an inactive C_5-diacid and which on Wohl degradation and oxidation gives a likewise inactive C_4-diacid. Arabinose could be shown by osazone formation to be the 2-epimer of ribose, and the configuration thus deduced. The 2-epimers xylose and lyxose are distinguished by the inactivity and activity of the respective C_5-diacids. The fact that arabinose and lyxose yield the same C_5-diacid provides confirmatory evidence.

Aldohexose Configurations. — An aid for remembering the names 16.16 of the eight D-aldohexoses is: All Altruists Gladly Make Gum In Gallon Tanks. Construct eight outline formulas, and under each write the name of the sugar in the order suggested: Allose, Altrose,

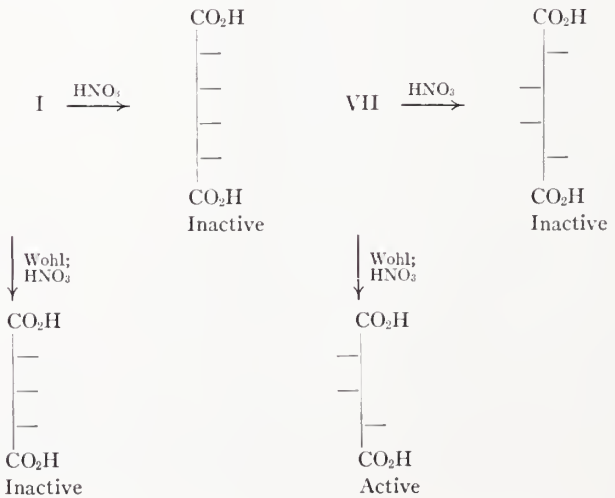
Glucose, Mannose, Gulose, Idose, Galactose, Talose. In the line corresponding to C_5, write a bar (or OH) to the right to signify that in each sugar (D-series) C_5-OH is to the right (and hydrogen to the left). In the line representing C_4, write four bars to the right and four to the left. At C_3 write OH twice to the right and twice to the left, and repeat the process; at C_2 write OH alternately to the right and to the left. The result is as shown.

The D-aldohexoses in epimer-pairs



16.17 The derivation automatically arranges the sugars in four pairs of 2-epimers, and it will be noted that on Wohl degradation the pair I–II yield ribose, III–IV arabinose, V–VI xylose, and VII–VIII lyxose. Configurations can be deduced from considerations like those cited above for the pentoses. Thus one of the eight D-aldohexoses is identified by the following observations: (a) the product of nitric acid oxidation is an optically inactive C_6-diacid; (b) the C_5-diacid resulting on Wohl degradation followed by nitric acid oxidation is optically active. Observation (a) shows that the sugar has the configuration I or VII, since these alone can give rise to C_6-diacids which are inactive. Of these two configurations, only VII can give an optically active C_5-

Deduction of formula of galactose



diacid, and hence the sugar, galactose, is identified as having the configuration VII.

Photosynthesis. — Carbohydrates arise in plants from fixation of carbon dioxide and absorption of water. The energy required is supplied in the form of solar energy absorbed by the plant. Photosynthesis can be expressed by a simple equation established in 1804 by de Saussure, who found that the amount of carbon dioxide absorbed by green plants is the molecular equivalent of the oxygen expired. The combination of carbon dioxide and water to form carbohydrate and oxygen is an endothermic reaction; burning of a carbohydrate or derivative is a reversal of photosynthesis and the liberation of heat represents a tapping of stored radiant energy.

16.18

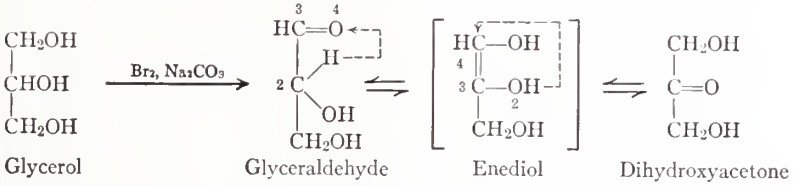
$$n\,CO_2 + n\,H_2O \xrightarrow{\text{Sunlight}} (CH_2O)_n + n\,O_2$$

$(CH_2O)_n$ → Hexose → Polysaccharide

SYNTHESIS AND METABOLISM OF SUGARS

Fischer's Synthesis. — Emil Fischer in 1890 had the insight to select for the chemical synthesis of DL-fructose a reversible reaction which, many years later, was found to be involved in a remarkable metabolic process. He elected to build the six-carbon chain by aldol condensation of two three-carbon units, glyceraldehyde and dihydroxyacetone. A mixture of the two components is obtained by merely oxidizing glycerol with bromine in sodium carbonate solution. Probably the primary alcohol group is oxidized first to give glyceraldehyde, but in a basic solution this, by a 2,4-hydrogen shift, is in equilibrium with an enediol which, by a similar shift, is in equilibrium with dihydroxyacetone.

16.19



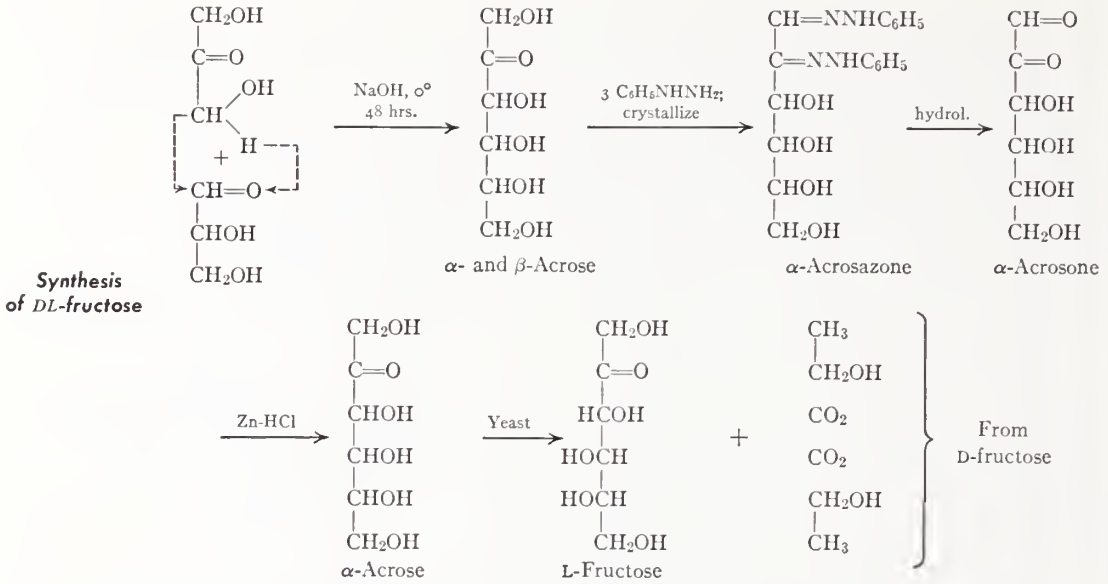
Glycerol — Glyceraldehyde — Enediol — Dihydroxyacetone

Starting materials

Fischer found that in the presence of a strong base the components of the easily prepared mixture undergo aldolization. An activated α-hydrogen atom of dihydroxyacetone adds to oxygen of the carbonyl group of glyceraldehyde and the terminal carbons become linked, and the result is the 2-ketohexose structure. The product was actually a mixture of two DL-sugars, which Fischer named α- and β-acrose. He effected separation by reaction with phenylhydrazine and crystallization, and so isolated pure α- and β-acrosazone. α-Acrose

16.20

Isolation through the osazone



Synthesis of DL-fructose

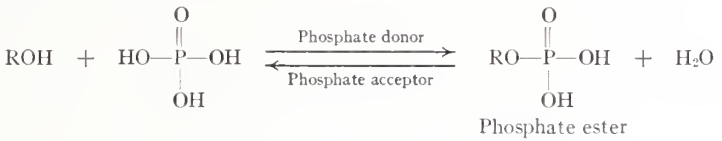
Regeneration from the osazone

was regenerated from its osazone by hydrolysis, which gives the ose-one (sugar-ketone) acrosone, and selective reduction of the more reactive aldehydic group. Optically inactive α-acrose could be any one of the four possible DL-2-ketohexoses. When submitted to fermentation with yeast, one component was converted into ethanol and carbon dioxide, the solution developed optical activity, and the product isolated had a specific rotation of $+92^\circ$ and proved to be the optical opposite, or enantiomer, of natural D-fructose, $[\alpha]_D -92^\circ$. α-Acrose was thus identified as DL-fructose, and, by further transformations permitting resolution, Fischer achieved the synthesis of a sugar identical with natural D-fructose. He also synthesized D-glucose.

Fermentation test

16.21 Alcoholic Fermentation. — It will be appreciated from the above formulation that the fermentation of a ketose to two molecules each of ethanol and carbon dioxide is a remarkable process. The carbon chain is cleaved at four places; certain carbon atoms become oxidized and others reduced, but there is no net gain or loss of any atoms. The overall reaction is $C_6H_{12}O_6 \longrightarrow 2\ CH_3CH_2OH + 2\ CO_2$, and the catalytic enzymes present in yeast operate so efficiently that the yield of the two products is 95% of that theoretically possible. Biochemical investigations extending over a period of years have elucidated each step in an elaborate cycle of transformations, most of which are reversible. Each step proceeds under the influence of one specific enzyme, and a technique for identifying an intermediate metabolite of the cycle consists in finding a way of deactivating the enzyme that effects destruction of the metabolite without deactivating the enzymes responsible for its production. Phosphoric acid is required for fermen-

tation, for most of the reactions of the alcoholic metabolites involve phosphate esters:



Phosphate esters of metabolites

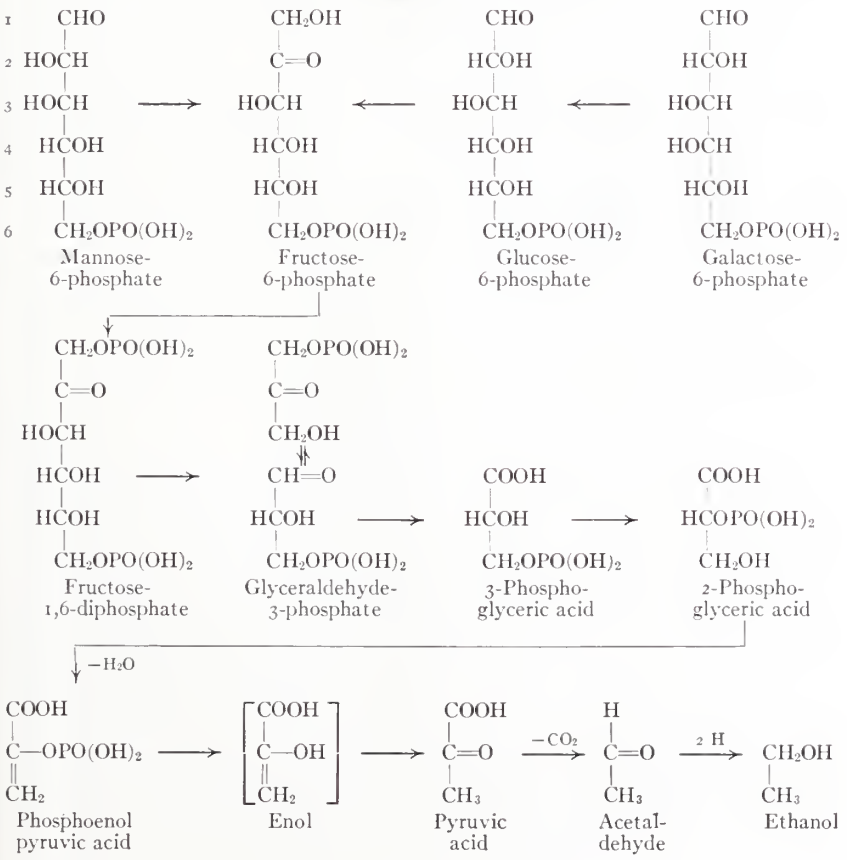
Phosphate donors and acceptors to form and hydrolyze the esters are further necessary components of the system.

The key pathway for fermentation of all four natural hexoses is through fructose-6-phosphate. The 6-phosphates of mannose and glucose are not fermented directly but are converted enzymatically into fructose-6-phosphate; the transformations probably involve equilibration with the common enediol, as in the base-catalyzed equilibrium between glyceraldehyde and dihydroxyacetone formulated above. Galactose is fermented at a substantially slower rate than glucose and mannose because it does not have the proper configuration at C_4 and must first be converted into glucose by inversion at C_4 (by oxida-

16.22

Fructose the key metabolite

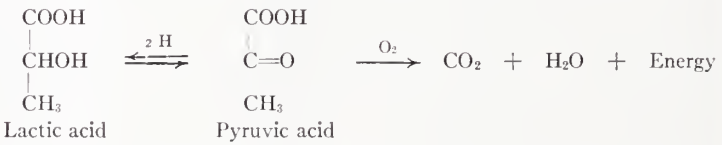
Interconversion of hexoses



tion to the ketone and reduction). The enzyme responsible for this reaction has been isolated and is named galactowaldenase (Walden inversion).

16.23 Fructose-6-phosphate next reacts with a phosphate donor to form the 1,6-diphosphate which, by reverse aldolization affords the phosphates of dihydroxyacetone and glyceraldehyde. The former phosphate is then enzymatically isomerized to glyceraldehyde-3-phosphate, which is oxidized to the corresponding acid. A specific enzyme then causes transfer of the phosphate group from position 3 to position 2. Water is eliminated with introduction of a double bond to give an enol phosphate. When a phosphate acceptor removes the phosphate group, the unstable free enol ketonizes to give pyruvic acid. Enzymatic decarboxylation gives acetaldehyde, which on reduction affords ethanol.

16.24 **Metabolism in Muscle.** — In muscle tissue, hexose is oxidized by oxygen to carbon dioxide and water as a source of muscular energy. Pyruvic acid is an intermediary metabolite, and it is formed from fructose-1,6-diphosphate in muscle by the same steps that are involved in fermentation. These steps are all reversible. The decarboxylation step of the fermentation process is irreversible. The enzyme of yeast which causes decarboxylation, carboxylase, is absent from muscle tissue, and hence acetaldehyde and ethanol are not formed in muscle tissue. Instead, pyruvic acid is in part reversibly reduced to lactic



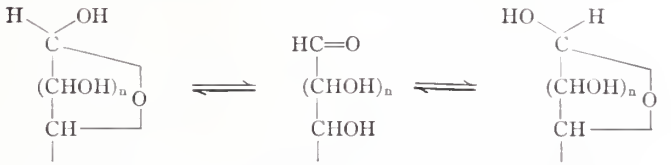
acid and in part oxidized, through a complex cycle of changes, with liberation of energy.

OXIDE STRUCTURE

16.25 **Two Forms of Glucose.** — Although glucose enters into some reactions common to aldehydes, such as addition of hydrogen cyanide, reaction with phenylhydrazine, and reduction of Fehling's solution, it reacts with bisulfite to a much lesser extent than ordinary aldehydes react. A further peculiarity is that a freshly prepared solution of glucose shows a rotation of $[\alpha]_D +113°$, which gradually decreases on standing to a value of $+52°$. This change is known as **mutarotation.** It is not the result of decomposition, for after mutarotation to a constant value material can be recovered that has all the properties of the original D-glucose and shows a specific rotation in a fresh solution of $+113°$. Fischer attributed the change to reversible hydration,

but this explanation became untenable when the French pharmacist Charles Tanret (1895) prepared an isomeric crystalline D-glucose by crystallization of the highly rotatory form from a concentrated aqueous solution at an elevated temperature (110°). The new form, named β-glucose, shows an initial rotation of $[\alpha]_D$ +19°, which changes slowly to the equilibrium value of +52°. The ordinary or α-form of glucose is obtained by crystallization from alcohol–water. The two forms have been shown to be cyclic oxides resulting from addition of one of the hydroxyl groups to the aldehydic carbonyl group; such an addition produces another center of asymmetry at C_1 and hence allows formation of two oxidic forms of glucose. Mutarotation of the sugar therefore is attributable to isomerization of one cyclic form into the other, probably by opening of the oxide ring to give the free aldehyde, and closure in the alternate steric sense by addition of the

α- and β-Cyclic forms



α-Form
$[\alpha]_D$+113°

Aldehydic form

β-Form
$[\alpha]_D$+19°

Equilibrium in solution

alcoholic hydroxyl to the carbonyl group. An aged solution of glucose thus contains α- and β-glucose in mobile equilibrium with the aldehydic form. Since the oxidic forms lack a carbonyl group, the response of glucose solutions to hydrogen cyanide, phenylhydrazine, and Fehling's solution must be due to the aldehydic form present in the equilibrium mixture; as this form enters into combination and is removed from the equilibrium mixture, more is formed at the expense of the oxides, and eventually the entire material is converted into the derivative of the aldehydic form. The equilibrium concentration of the reactive species is less than 0.01%, and hence conditions are unfavorable for reversible addition of sodium bisulfite, and equilibrium is reached at a point of low conversion.

The point of attachment of the oxide ring to the carbon chain was established in investigations of the more stable 1-methyl ethers of α- and β-glucose, known as α- and β-methylglucoside. Treatment of

16.26



α-Methylglucoside
$[\alpha]_D$+159°

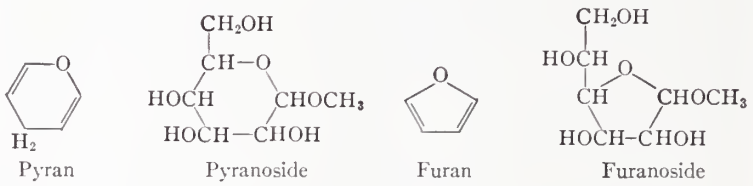
β-Methylglucoside
$[\alpha]_D$−34°

α- and β-Methylglucoside

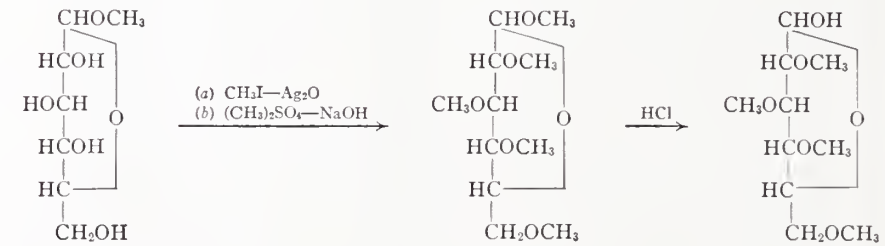
glucose with methanol and hydrogen chloride affords chiefly α-methylglucoside (Fischer, 1893), along with a smaller amount of the β-isomer (van Ekenstein, 1894). The methylglucosides do not react with carbonyl reagents and do not exhibit mutarotation, since the labile glucosidic hydrogen atom is replaced by methyl.

16.27 A cyclic ether of glucose is called a glucoside, and a cyclic derivative of mannose is called a mannoside; the generic name for a cyclic sugar derivative is glycoside. A glycoside having the six-membered ring of pyran is called a pyranoside and one corresponding to furan a furanoside. The furanoside structure was regarded as the more

Pyranose (6) and furanose (5) rings

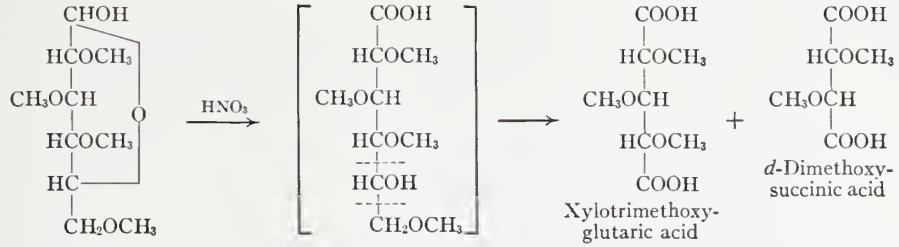


likely for the glucose derivatives until 1926 when W. N. Haworth and E. L. Hirst in England presented evidence that methylglucoside is a pyranoside. Methylglucoside can be methylated with methyl iodide and silver oxide or with dimethyl sulfate in an alkaline medium to form a pentamethyl derivative in which four of the methyl groups are present in stable ether linkage. The glucosidic methyl group is hydrolyzed readily by dilute acids, but not by alkali, with formation of tetramethylglucose. Hirst oxidized tetramethylglucose with nitric acid and obtained in good yield xylotrimethoxyglutaric acid and *d*-



Proof of pyranoside structure

dimethoxysuccinic acid (identified as the diamides). Formation of these two acids shows that cleavage occurs at each side of C_5 and hence that this is the site of the one free hydroxyl group and hence the location of the oxide ring. Methylglucoside is thus characterized as a pyranoside, and glucose as a pyranose. The other hexoses in their normal forms have been shown to be pyranoses.

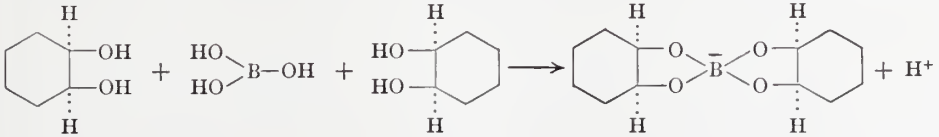


Tetramethyl-D-glucose

Xylotrimethoxyglutaric acid

d-Dimethoxysuccinic acid

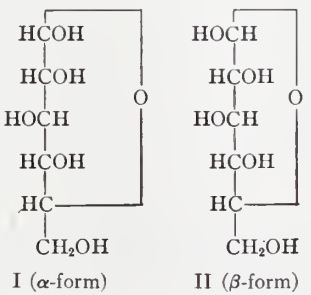
Configuration and Conformation. — A water-soluble *cis*-glycol added to a solution of boric acid increases the electrical conductivity of the solution because it forms an ionic complex with the inorganic acid: **16.28**



***cis*-Glycol**

The α-form of glucose, α-D-glucopyranose, produces such an increase in conductivity, and the conductivity decreases with time as the α-form is converted to an equilibrium mixture. The β-form has little initial effect, but the conductivity gradually increases. The α-form thus contains a *cis*-glycol grouping, and, since the hydroxyls at C_2-C_3 and at C_3-C_4 are *trans*, the glycosidic hydroxyl at C_1, defined as an anomeric hydroxyl, must be *cis* to the hydroxyl at C_2, as in formula I. Formula II is assigned to the β-form, the full name of which is β-D-glucopyranose.

Anomeric hydroxyl

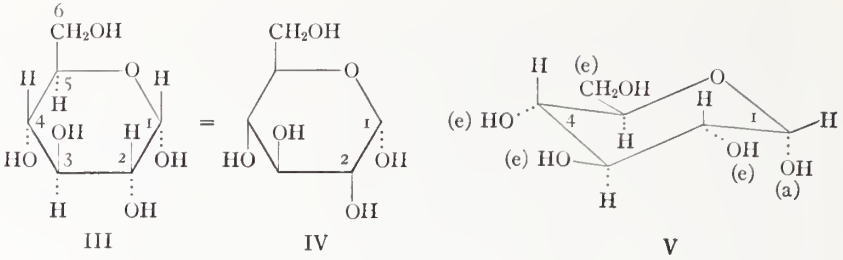


I (α-form) II (β-form)

D-Glucopyranose

Stereochemical relationships are appreciated best by translation of formulas of the type I–II into hexagons (W. N. Haworth, 1929). The operation can be done somewhat laboriously with Fischer tetrahedral projections but easily with models, and the result, for α-glucose, is formula III. The anomeric hydroxyl at C_1 is α, or down, as indicated **16.29**

Haworth formulas; conformation



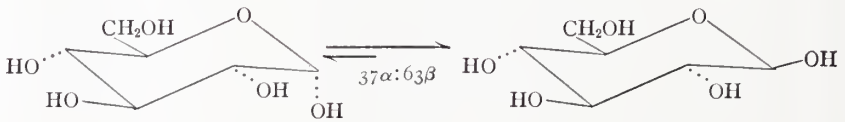
III IV V

α-D-Glucopyranose

by the dotted bond, and the C_2-OH being *cis* to it is also α, or down. The rest of the formula is easily derived by remembering that the hydroxyls at 2,3 and at 3,4 are *trans* to each other and that C_4-OH is *trans* to C_5-CH_2OH. The formula can be simplified (IV) by omitting the hydrogen atoms and indicating the configuration of just the anomeric hydroxyl, in this case α (dotted bond).

16.30 Formula V shows the preferred conformation of α-glucose, established by study of cuprammonium complex formation (1949). The hydroxyls at C_2, C_3, C_4 and the C_5-CH_2OH group are all in the stable equatorial orientation and only the anomeric hydroxyl is axial. In β-glucose (VI) the anomeric hydroxyl is equatorial, and hence this anomer would be expected to have the greater stability. That this is the case is shown by the specific rotations of the α (+113°) and

All-equatorial form the more stable

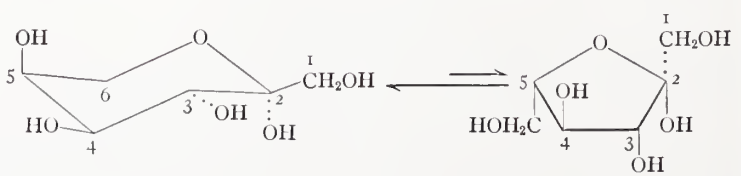


V (α) VI (β)

β (+19°) forms and of the equilibrium mixture (+52°). The stable, all-equatorial conformation of β-glucose may account for the widespread occurrence of β-glucosides in nature. Glucose is the only one of the eight D-aldohexoses in which the all-equatorial arrangement is possible.

16.31 Fructose is known in only one crystalline form, probably the pyranose VII. That fructose exhibits mutarotation (−132° ⟶ −92°) is attributed to an equilibrium with fructofuranose, VIII. Although

Fructopyranose and furanose

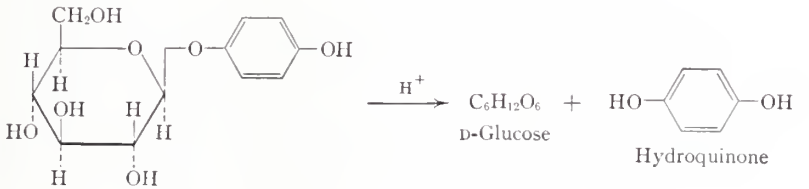


VII VIII

VIII has not been isolated, this is the form in which fructose occurs in sucrose and in all other natural fructosides.

GLYCOSIDES

16.32 Plant glycosides are comparable to methylglucosides, and are derived from combination of various hydroxy compounds with various sugars. They are designated specifically as glucosides, mannosides, galactosides, etc., and the group as a whole is described by the generic name glycoside. When a sugar is combined with a nonsugar, the latter is described as an aglycone. When the second group is also a sugar unit, the combination is a di-, tri-, or polysaccharide. The glycosides are hydrolyzed by mineral acids to the sugar and the aglycone; for instance arbutin, a β-D-glucoside obtained from the bearberry (*Arctostaphylos uva-ursi*), yields glucose and hydroquinone on hydrolysis:



Arbutin

Hydrolyzed to sugar and aglycone

Usually an enzyme that can accomplish the hydrolysis occurs in the same plant, though in different cells. When the plant tissues are macerated the enzyme comes into contact with the glycoside and hydrolysis results. Although some enzymes can act on only one substance (substrate), many are not specific in activity. The widely distributed emulsin and maltase both hydrolyze many glycosides, but the differentiation first noted by Fischer, namely that the former acts on β-glucosides and the latter on α-glucosides, is true for α- and β-glycosides generally, and is frequently used as a proof of the type of glycoside linkage. Most natural glycosides possess the β-configuration.

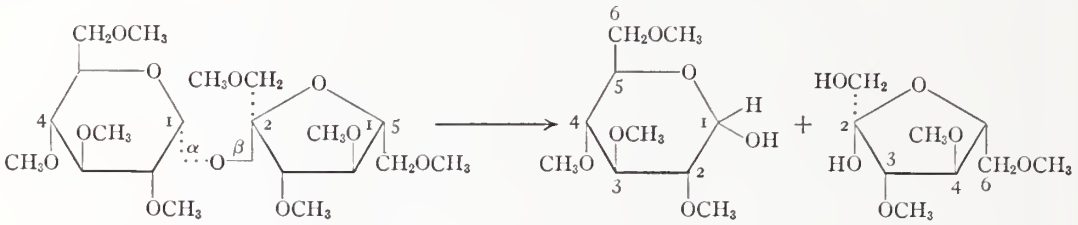
DISACCHARIDES

16.33 Disaccharides can be regarded as glycosides in which the aglycone is a second monosaccharide unit. They resemble monosaccharides in that they are very soluble in water, and some have a sweet taste. Only three occur as such in nature, sucrose (cane sugar), lactose (milk sugar), and maltose, and the latter is found free only occasionally.

16.34 **Sucrose.** — Sucrose on hydrolysis with acids or the enzyme invertase (plants, yeast, animals) yields D-glucose and D-fructose in equal amounts. Sucrose does not reduce Fehling's solution or form deriva-

tives with phenylhydrazine, and hence the two sugar units are linked through the glycosidic hydroxyl group of each sugar and contain no free or potential carbonyl groups. Unlike the majority of sugars, sucrose crystallizes readily, probably because it does not isomerize in solution (no mutarotation). The ring structure of the two component units was established (Haworth, 1916) by hydrolyzing completely methylated sucrose (I). One product was the usual tetra-

Structure by methylation and cleavage

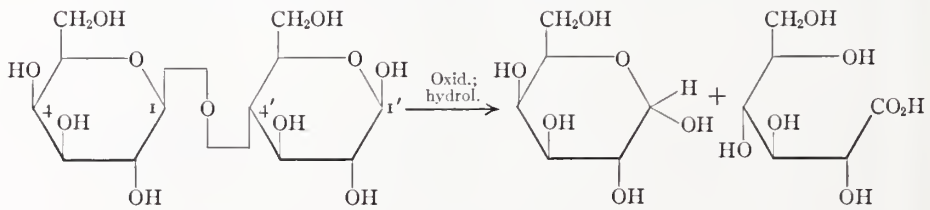


I Octamethylsucrose II (α,β) III

methyl-D-glucose, but the other was a tetramethylfructose derivative. Its structure was not established until ten years later, when it was found to contain a furanose ring (III). No combined fructose has ever been found to have the normal pyranose structure. The glucose unit has the α-configuration, since sucrose is hydrolyzed by maltase (an α-glucosidase); the configuration of the fructose unit is considered to be β.

16.35 Lactose. — Lactose occurs in the milk of mammals; human milk contains 5–8%, cow's milk, 4–6%. It is produced commercially from the latter source as a by-product in the manufacture of cheese. Lactose is a reducing sugar, forms an osazone, and can be obtained in crystalline α- and β-forms, $[\alpha]_D$ +90° and $[\alpha]_D$ +35°. It is hydrolyzed by dilute mineral acid or by emulsin to glucose and its 4-epimer, galactose. Since the acid obtained on bromine oxidation of lactose is hydrolyzed to galactose and gluconic acid, the reducing group must be in the glucose unit, and hence lactose is a galactoside and not a

A reducing β-glycoside

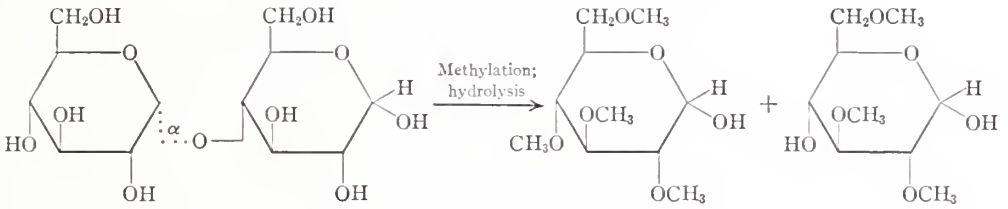


Lactose, β-form Galactose (α,β) Gluconic acid

glucoside. Hydrolysis by emulsin shows the sugar to be a β-galactoside, and methylation experiments show the 1β-galactosido link to be joined to the 4′-hydroxyl of glucose. If the hexose units are written in the usual way with the oxidic oxygen up, connection has to be

made between the 1β-glucosidic link, which is up, and the 4′-OH, which is down. This can be done with the run-around glycosidic link shown in the formula; the alternate, less convenient representation requires inversion of one of the hexagons.

Maltose. — Maltose is obtained in about 80% yield by enzymatic (amylase) degradation of starch. Since the disaccharide yields only ——— 16.36

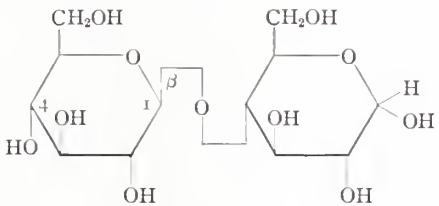


Maltose

D-glucose on hydrolysis with acids or maltase, an α-glucosidase, it is evidently a glucose-α-glucoside. It is a reducing sugar, and hence contains one potential aldehydic group. Methylation studies established the structure as that of glucose-4-α-glucoside.

A reducing α-glucoside

Cellobiose. — Cellobiose can be obtained by hydrolysis of cellulose. It is a reducing sugar consisting of two glucose units and hydrolyzable by emulsin, a β-glucosidase; thus it is a glucose-β-glucoside. Methylation studies have shown that cellobiose is related to maltose in the same way that β-methylglucoside is related to the α-isomer. ——— 16.37



Cellobiose (α,β)

A reducing β-glucoside

POLYSACCHARIDES

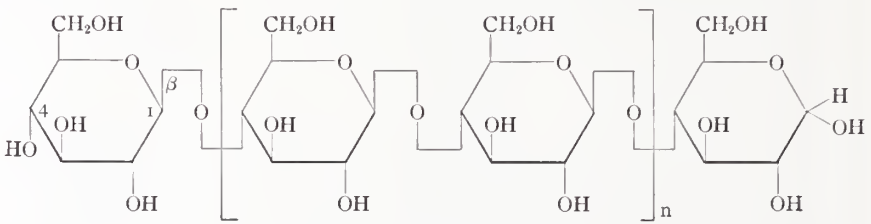
Polysaccharides belong to two general groups: those that are insoluble and form the skeletal structure of plants and of some animals; and those that constitute reserve sources of simple sugars, which are liberated as required by the action of enzymes present in the organism. Both types are high molecular weight polymers, often built up from a single pentose or hexose unit. In this respect they differ from the proteins, which are high molecular weight substances containing several different units. ——— 16.38

Cellulose. — Cellulose is the most widely distributed skeletal polysaccharide. It constitutes approximately half of the cell-wall ——— 16.39

material of wood and other plant products. Cotton is almost pure cellulose and, together with bast from flax, is the preferred source of cellulose for use as fiber. Wood cellulose, the raw material for the pulp and paper industry, occurs in association with lignin, a nonpolysaccharide which is separated by treating wood with an alkali bisulfite to form water-soluble lignosulfonates.

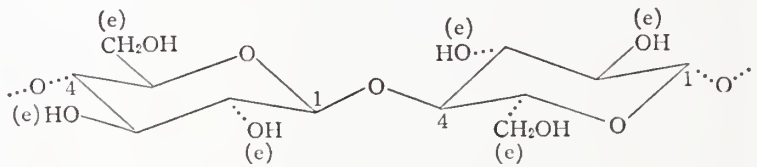
16.40 Cellulose on drastic hydrolysis affords glucose. Under milder conditions mixtures are formed from which cellobiose, cellotriose, and cellotetrose have been isolated; hence cellulose has the structure shown. The most stable conformation is that in which the three sub-

Structure



Cellulose

Conformation



stituents in each six-membered ring, as well as the 1- and 4-glucosidic linkages, are all equatorial. The average molecular weight of cellulose is 400,000, corresponding to 2500 glucose units. X-ray analysis indicates that cellulose fiber is made up of micelles, or bundles of parallel oriented chains probably held together by hydrogen bonding. The diameter of a micellar unit is about 40Å, corresponding to 100–200 cellulose chains; the length is at least 600Å, corresponding to 200 glucose units. The mechanical strength and chemical stability are considered to result from micellar structure.

Micellar structure of fiber

16.41 Man and other carnivorous animals are unable to utilize cellulose, since they lack enzymes required for hydrolysis. Many microorganisms, some protozoa, and the snail can decompose cellulose. Digestion of cellulose by ruminants (cud-chewing animals) is due to the presence of microorganisms within the specially constructed alimentary system.

SUMMARY

Classification of carbohydrates: mono-, di-, polysaccharides. Sugar = -ose. Aldo- and keto-pentoses, hexoses. Inversion of sucrose. Proof of structures of glucose and fructose. Ability to reduce Fehling's solution characteristic of α-hydroxy ketones as well as of aldehydes.

Acetylation reveals 5 OH-groups. Carbon skeleton and position of carbonyl group established by formation of cyanohydrin, hydrolysis, reduction of hydroxyl group, identification of resulting acid.

Configurations of natural hexoses: glucose, mannose, galactose, fructose (E. Fischer, 1896). Configuration of glucose at C_5 correlated with that of D-tartaric acid and of D-glyceraldehyde (OH to the right, H to the left). Natural hexoses all belong to the D-series, even levorotatory fructose, or D-(−)-fructose. Of the sixteen aldohexoses, only the three natural ones are fermentable; fructose, only natural ketohexose, also fermentable.

Osazones (Fischer, 1884). Reaction of a reducing sugar with three molecules of phenylhydrazine to give a crystalline yellow osazone sparingly soluble in water and easily isolated. Reaction destroys asymmetry at C_2, hence glucose and mannose give same osazone, which is formed also from fructose.

Cyanohydrin synthesis (Kiliani). Addition of HCN to aldose and hydrolysis gives an acid that forms γ-lactone reducible with Na—Hg to a new aldose. Thus aldopentose ——→ aldohexose.

Reduction of glucose gives sorbitol. NaOBr attacks aldehydic group ——→ gluconic acid. HNO_3 attacks both terminal groups ——→ glucosaccharic acid (dibasic).

Wohl degradation. Aldose ——→ oxime ——→ cyanohydrin ——→ lower aldose. Glucose ——→ arabinose ——→ erythrose. Erythrose with HNO_3 ——→ mesotartaric acid. On similar degradation galactose ——→ D-(−)-tartaric acid.

D-Tetroses. Erythrose on HNO_3 oxidation gives optically inactive C_4-diacid (*meso*, plane of symmetry). Threose gives active acid (no symmetry). D-Pentoses (RAXL): ribose and arabinose (C_2-epimers related to erythrose); xylose and lyxose (C_2-epimers related to threose). Deduction of configurations from activity or inactivity of derivable C_5- and C_4-diacids.

D-Aldohexoses. Memory aid (All Altruists Gladly . . .) and system for deriving names and formulas. Deduction of the configuration of D-galactose: (*a*) on nitric acid oxidation, the hexose gives an optically inactive C_6-diacid; (*b*) Wohl degradation of the hexose followed by nitric acid oxidation gives an optically active C_5-diacid.

Synthesis and Metabolism

Fischer's synthesis. Glycerol on mild oxidation gives glyceraldehyde which, in sodium carbonate solution, is in equilibrium with dihydroxyacetone through a common enediol. A strong base causes aldol condensation to a mixture of 2-ketohexoses from which α- and β-acrose were isolated as the osazones. α-Acrosazone hydrolyzed to α-acrosone and this reduced at the aldehyde group to give α-acrose, shown to be DL-fructose by action of yeast to give unfermented residue of L-fructose. By further transformations, Fischer resolved DL-fructose and achieved the synthesis of natural D-fructose.

Alcoholic fermentation:

$$C_6H_{12}O_6 \longrightarrow 2\ CH_3CH_2OH + 2\ CO_2.$$

A cyclic process of many steps, each controlled by an enzyme and proceeding through phosphate esters of metabolites. Fructose-6-phosphate, formed by isomerization of 6-phosphates of glucose, mannose, and (more slowly) galactose, is converted into fructose-1,6-diphosphate which, by reverse aldolization, yields the phosphates of dihydroxyacetone and glyceraldehyde. Glyceraldehyde-3-phosphate then oxidized to the acid, the phosphate group migrates from C_3 to C_2, water is eliminated to form the phosphate of enolpyruvic acid. The free enol ketonizes, decarboxylation of free pyruvic acid gives acetaldehyde, which on reduction affords ethanol.

Metabolism in muscle. Pyruvic acid is formed as in fermentation, but the decarboxylation enzyme of yeast is absent from muscle tissue and pyruvic acid is in part reversibly reduced to lactic acid and in part oxidized to carbon dioxide and water with liberation of energy.

Oxide Structure

Glucose fails to respond to some reagents for aldehydes and exhibits mutarotation ($[\alpha]_D$ +113° for fresh solution, +52° for aged solution). Existence of two forms: α-glucose (ordinary, initial $[\alpha]_D$ +113°) and β-glucose (crystallization from water at 110°, initial $[\alpha]_D$ +19°). Addition of OH group to carbonyl group to give cyclic oxide with new center of asymmetry at C_1.

α- and β-Methylglucoside from glucose + CH_3OH + HCl (α-predominates). Generic name: glycoside. Nonreducing, no reaction with phenylhydrazine, no mutarotation. Possible forms: pyranoside (6-ring), furanoside (5-ring). Proof of pyranose structure: methylglucoside ——→ pentamethyl derivative; acid hydrolysis removes glycosidic 1-OCH_3 and gives tetramethylglucose in which OCH_3 groups

are shown to be at 2, 3, 4, and 6; hence the oxide link extends to C_5.

α-Glucose (α-D-glucopyranose) shown to be C_1-C_2 *cis*-glycol from conductivity of boric acid solution (complex).

Haworth hexagon formula for α-D-glucopyranose and abbreviation: write dotted (α) or full (β) bonds for just the anomeric linkage to OH at C_1. Conformations: β-form the more stable since all OH groups and CH_2OH are equatorial. D-Fructose probably a pyranoside, which in solution mutarotates through equilibrium with furanoside form.

Glycosides

Hydroxy component (aglycone) combined with a sugar (or polysaccharide). Hydrolyzed by HCl, also by enzymes: emulsin splits β-glucosides, maltase splits α-glucosides. Example: arbutin (hydroquinone + β-D-glucose).

Disaccharides

Sucrose. Nonreducing, no osazone, no mutarotation (therefore crystallizes readily). Structure: pyranose form of α-glucose (α-glucopyranoside) linked at C_1 to furanose form of β-fructose (β-fructofuranoside) at C_2: 1α-glucosido-[1,5]-2-fructoside-[2,5]. Inertness due to utilization of glycosidic OH groups of both components. Proof of structure: octamethylsucrose hydrolyzed to 2,3,4,6-tetramethylglucose and 1,3,4,6-tetramethylfructose. Stable form of fructose has pyranose structure, but combined fructose always occurs in the furanose form.

Lactose. Galactose, in glycosidic form, linked to glucose at C_4: 1β-galactosido-[1,5]-4-glucose. The glucose part has a free or potential carbonyl group, and hence lactose is a reducing sugar and forms an osazone.

Maltose. Corresponds to lactose except that the β-galactosido group is replaced by an α-glucosido group. A reducing sugar hydrolyzable to two molecules of glucose.

Cellobiose. Corresponds to lactose except that the galactosido group is replaced by a β-glucosido group (β-isomer of maltose).

Polysaccharides

Cellulose. Pure forms: cotton, filter paper. From wood by extraction of lignin with sulfite. Hydrolyzed with difficulty by acids to glucose. Partial hydrolysis yields cellobiose, cellotriose, cellotetrose and thus reveals structure: β-glucosido units linked head-to-tail at positions 1 and 4. Molecular weight, 400,000. Indicates chains of about 2500 glucose units. X-ray pattern shows that fiber contains bundles of parallel oriented chains (micelles).

PROBLEMS

1. A certain pentose, which forms a tetraacetate, is condensed with hydrogen cyanide and the product is hydrolyzed and reduced with HI–P. The resulting acid is identical with one synthesized from $CH_3CH_2CH_2I$ and $CH_3CH(CO_2C_2H_5)_2$. What is the structure of the pentose?
2. Study of the natural sugar rhamnose limited the possible structures to formulas (*a*) and (*b*). Suggest an oxidation experiment by which a distinction could be made between the two formulas.

   (*a*) $CH_3CHOHCHOHCHOHCHOHCHO$
   (*b*) $HOCH_2CH_2CHOHCHOHCHOHCHO$

3. What test would distinguish between a 2-desoxyhexose (*a*) and a 3-desoxyhexose (*b*)?

   (*a*) $HOCH_2CHOHCHOHCHOHCH_2CHO$
   (*b*) $HOCH_2CHOHCHOHCH_2CHOHCHO$

4. What tests would distinguish between the isomers (*a*), (*b*), and (*c*)?

   (*a*) $HOCH_2CHCHOHCHOHCHOHCHOCH_3$ (O bridge)

   (*b*) $HOCH_2CHCHOHCHOHCH(OCH_3)CHOH$ (O bridge)

   (*c*) $HOCH_2CHCHOHCH(OCH_3)CHOHCHOH$ (O bridge)

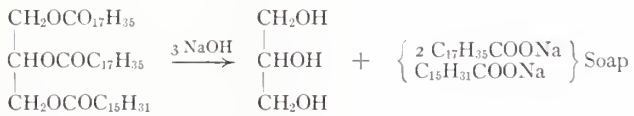
5. Two aldotetroses, A and B, give the same osazone, but on oxidation with nitric acid A gives an optically inactive C_4-diacid and B gives an optically active C_4-diacid. Identify A and B.
6. How could D-galactose be distinguished from its 2-epimer, D-talose?

CHAPTER 17

LIPIDS

17.1

Constituents of plant or animal tissue that are insoluble in water but soluble in ether or other water-immiscible organic solvents are known as lipids. The most abundantly occurring lipids are animal fats (tallow, lard) and vegetable oils (olive, castor); such lipids are called neutral fats. These substances, which are either oils or low-melting solids with a greasy feel, are glycerides in which glycerol is esterified with two or three higher fatty acids, such as stearic (C_{18}) and palmitic (C_{16}) acid. Hydrolysis of a glyceride with hot aqueous



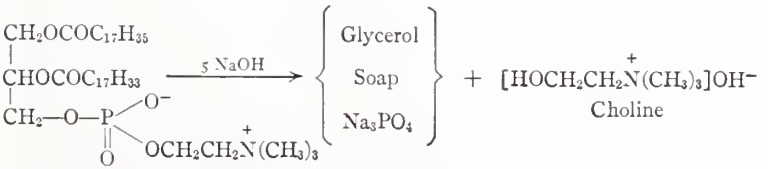
Typical glyceride

Saponification of a fat

alkali is called saponification (L. *sapo*, soap) because one product, a mixture of the sodium salts of the component fatty acids, is a soap. Saponification reverses the solubility relations, since at suitable dilution the products are soluble in water and not extractable with ether.

17.2

The tissues of brain and spinal cord contain complex structural units constructed from protein, cholesterol, and phospholipids of a type exemplified by the lecithins. A lecithin is a glyceride containing two, usually different, fatty acid residues (e.g., stearic acid and its unsaturated derivative oleic), and a phosphocholine group, which on



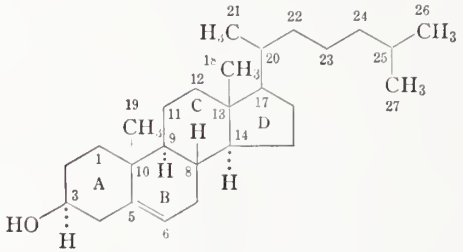
Typical lecithin

Saponification of lecithin, a phospholipid

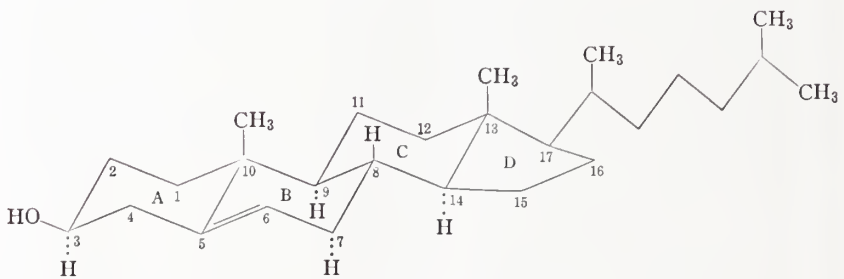
saponification affords inorganic phosphate and the quaternary base choline.

17.3 **Nonsaponifiable lipids.** — When brain tissue is saponified, the phospholipids, fats, and proteins are converted largely into water-soluble, ether-insoluble products and extraction of the alkaline mixture with ether affords a nonsaponifiable lipid fraction of which cholesterol, $C_{27}H_{45}OH$, is the main component. Cholesterol, a crystalline solid

Cholesterol



Cholesterol, m.p. 149°



Cholesterol, conformation

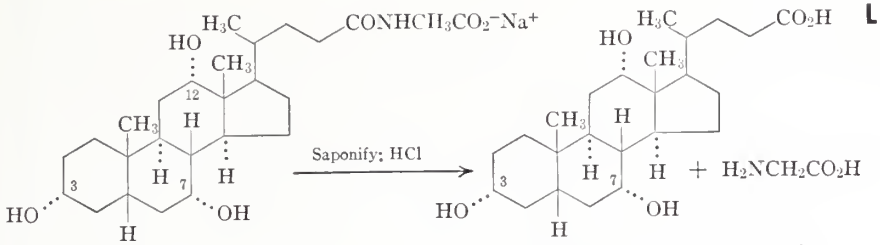
of fairly high melting point, has the structure and steric configuration shown in the first formula. The second formula shows the conformation; the three six-membered rings (A, B, C) have the chair conformation. The secondary alcoholic group at C_3 in ring A is oriented to the front (full-line bond, β), as are the angular methyl groups at C_{10} and C_{13} and the side chain at C_{17}. Ring B contains a double bond.

17.4 Cholesterol results from saponification and extraction of all body tissues, including blood, which normally contains about 200 mg. of total cholesterol per 100 ml. Some 27% of the blood cholesterol is present as such and the rest is esterified with higher fatty acids such as stearic, oleic, palmitic. The total cholesterol in a man weighing 170 lbs. amounts to about 250 g. It is derived in part by biosynthesis in the body and, in carnivorous animals, from the diet. Egg yolk is a rich source of cholesterol; the water-insoluble lipid is emulsified by the lecithin present.

Distribution in the body

17.5 Bile acids are the next most abundant nonsaponifiable lipid constituents of the body. Bile contains about 6% of a mixture of bile salts of the type formulated. Saponification cleaves the amide

Bile acids



A bile salt — Cholic acid (bile acid) — Glycine

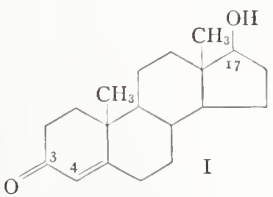
linkage to give, after acidification, the free bile acid and glycine. Cholic acid is the major component of the mixture of bile acids isolable from human bile. The bile salt formulated is thus the salt of the conjugate acid from cholic acid and glycine, one of the building units of proteins. The major portion of the molecule is largely hydrocarbon in character, or lipidlike, and this is balanced by a small ionic group $—CO_2^-Na^+$, which is water-seeking, or hydrophilic. A bile salt is thus a surface-active agent. It has a lipophilic-hydrophilic balance just appropriate for bringing water-insoluble lipids into colloidal dispersion in water. This, indeed, is the function of bile salts. Bile secreted into the intestine emulsifies the neutral fats (glycerides) of the diet and so facilitates their absorption through the intestinal wall into the blood stream.

Bile salts emulsify neutral fats

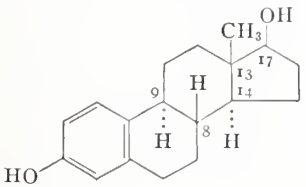
Present in the body in trace amounts, in comparison to cholesterol and the sterol-like or steroid bile acids, are a number of steroid hormones. These are substances secreted by certain glands to control specific processes of growth essential to healthful functioning of the body. The gonads (sex glands) produce the sex hormones testosterone (C_{19}), estradiol (C_{18}), and progesterone (C_{21}); the cortex of the adrenal gland produces adrenal cortical hormones such as cortisone

17.6

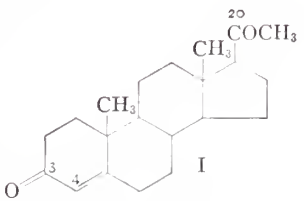
Steroid hormones



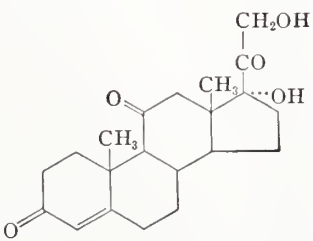
Testosterone



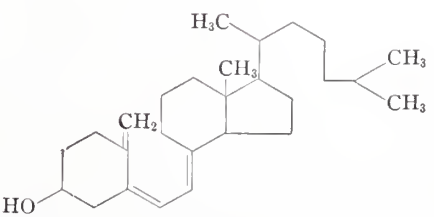
Estradiol



Progesterone



Cortisone



Vitamin D_3

(C_{21}). The nonsaponifiable lipid fraction of urine contains a shower of products of metabolism of steroid hormones. Each steroid hormone has a specific physiological action, and the amount of material normally required to produce the effect is extremely small. These hormones have been isolated from the nonsaponifiable fractions of glands or of urine only by processing very large amounts of tissue. For example, in the first isolation of progesterone by Adolf Butenandt in Germany, 625 kg. of ovarian tissue from 50,000 sows afforded 20 mg. of the pure hormone.

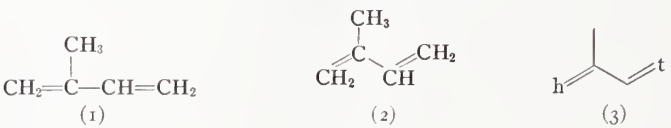
Isolation difficult

17.7 One of the vitamins, that is, growth factors derived in whole or in part from the diet, is a sterol related to cholesterol, namely vitamin D_3, which has been isolated from fish liver oils. The body requires only 5γ (0.005 mg.) of this vitamin per day; dietary deficiency leads to rickets, a disease characterized by softening of the bone.

A steroid vitamin

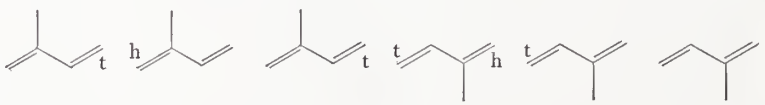
17.8 Several other nonsaponifiable lipids that occur in trace amounts in specific tissues have in common the feature that the structures are divisible in whole or in part into isoprene units. Isoprene is a diene of the formula C_5H_8 resulting from the destructive distillation of rubber. Rubber is one of many natural products describable as

Isoprenoid types

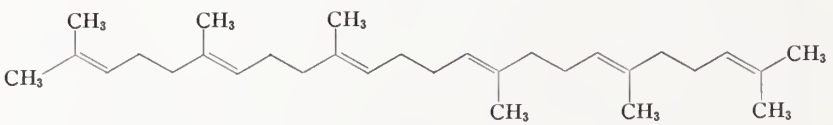


Isoprene

isoprenoids because they are made up of isoprene units. The formulas of isoprenoid nonsaponifiable lipids are derived most easily by use of the formula (2), or the abbreviation (3), in which one terminal carbon can be designated a head position (h) and the other a tail (t). Squalene, an unsaturated hydrocarbon of the formula $C_{30}H_{50}$ found in shark liver oil, contains six isoprene units joined thus: t—h, t—h, t—t, h—t, h—t. The structural formula as written suggests the



Isoprene units



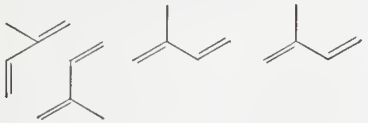
Squalene

possibility that the long branched chain is formed by 1,4-addition of isoprene units; the six double bonds are all *trans*. Squalene belongs to a group known as carotenoids after the prominent member β-

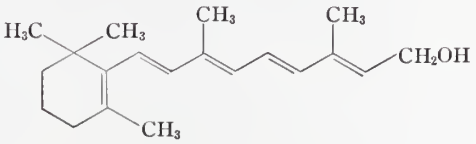
carotene, a pigment which occurs in the carrot, in green leaves, and in blood, and which owes its color (red, dilute solutions yellow) to the presence of eleven conjugated double bonds. β-Carotene, $C_{40}H_{56}$, is oxidized in the liver and suffers fission at its central link to produce vitamin A, $C_{20}H_{30}O$, a factor isolated from fish liver oils which plays a role in photoreception in the retina. It is a primary allylic alcohol derived from four isoprene units joined tail to head.

β-Carotene

Vitamin A



Isoprene units

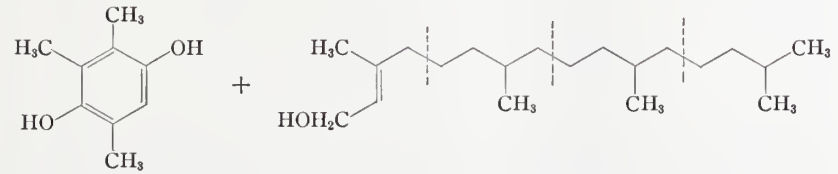


Vitamin A

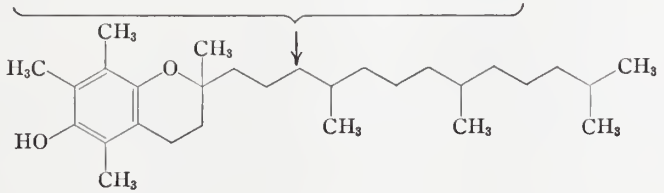
α-Tocopherol, a vitamin E factor which counteracts sterility in rats but which is not known to be essential to man, has been isolated from the nonsaponifiable lipid fractions of wheat germ oil and of liver. Synthesis is accomplished by condensation of trimethylhydroquinone

17.9

α-Tocopherol



Trimethylhydroquinone Phytol

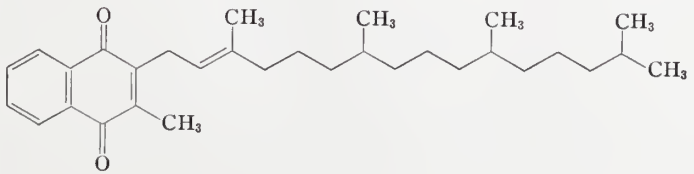


α-Tocopherol

with phytol, an allylic, isoprenoid alcohol ($C_{20}H_{40}O$) which is liberated on saponification of an ester grouping of chlorophyll, the pigment of green plants.

Vitamin K_1 also contains a phytyl group, which in this case is linked to a quinone ring. It is likewise synthesized from phytol,

17.10



Vitamin K_1

Vitamin K_1

and it is used in therapy to promote normal clotting of the blood, for example, in newborn babies subject to bleeding to death from a pin prick because they have not yet acquired adequate antihemorrhagic factor from the diet. Operation for removal of a cancerous growth obstructing the flow of bile may be attended by dangerous bleeding because, in the absence of emulsifying bile salts, K_1 is not absorbed from the diet. The deficiency can now be corrected prior to operation by intravenous injection of a water-soluble derivative of synthetic vitamin K_1.

GLYCERIDE FATS AND OILS

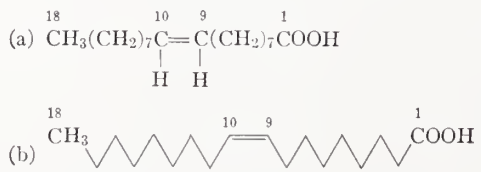
17.11 Component Fatty Acids. Saponification of a fat of either animal or plant source gives a mixture of fatty acids, saturated and unsaturated. All the acids have a straight chain containing an even number of carbon atoms; odd-carbon and branched-chain acids are not components of natural fats. The most abundant saturated acids are those in the series C_{12}–C_{18}. Stearic and palmitic acid occur abundantly in beef and pork fat glycerides, and the latter but not the former acid is a major constituent of palm oil (43%) and occurs in almost all fats. Lauric acid is the most abundant acid derived from coconut oil (48%) and related oils. Myristic acid is usually a minor component; it can be isolated readily from the nutmeg.

Common saturated acid components

Acid	Formula	M.p.
Lauric	n-$C_{11}H_{23}CO_2H$	44°
Myristic	n-$C_{13}H_{27}CO_2H$	58°
Palmitic	n-$C_{15}H_{31}CO_2H$	63°
Stearic	n $C_{17}H_{35}CO_2H$	70°

17.12 The three most common unsaturated acids from fats are C_{18}-compounds which are hydrogenable to stearic acid and which contain one (oleic), two (linoleic), and three (linolenic) double bonds. The most abundant of these is oleic acid, which is the major acid of olive oil (83%) and is also the major acid of the depot fats of herbivorous animals: mutton and beef tallow (48%), neat's-foot oil from ox hoof (80%). Oleic acid has a double bond at the center of the 18 carbon chain and this bond has the *cis*-configuration. The formula is often written as in (a), but the simplified representation (b) has the ad-

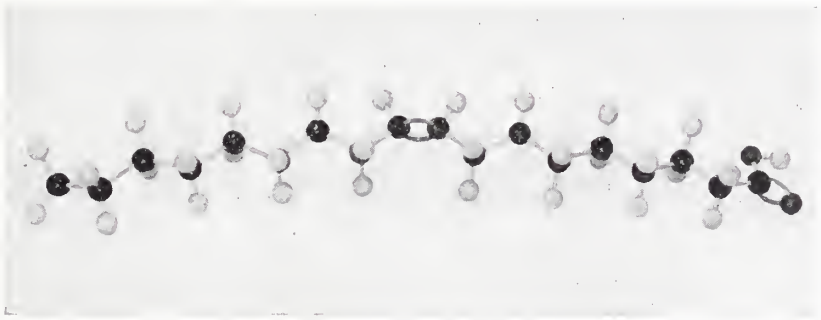
Unsaturated acids (C_{18})



Oleic acid (m.p. 13°, 16°)

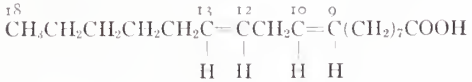
vantage of showing better the *cis*-character of the double bond and the zig-zag alignment of the carbons in the two attached chains, evident from the photograph. Oleic acid is lower melting and less

cis-Configuration

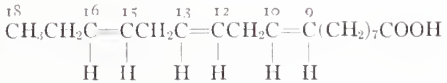


Model of oleic acid

stable than the *trans*-isomer elaidic acid (m.p. 44°), into which it can be isomerized. Linoleic acid and linolenic acid conform to the oleic pattern in having one double bond at the 9,10-position. Both have a second double bond at C_{12}–C_{13}, and linolenic acid has a third

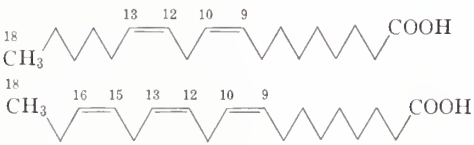


Linoleic acid (m.p. −5°)



Linolenic acid (m.p. −11°)

one at C_{15}–C_{16}; the hydrocarbon half of the chain is thus divided into three three-carbon units. All the double bonds in the two acids have the *cis*-configuration, as emphasized in the simplified formulas.



Linoleic acid

Linolenic acid

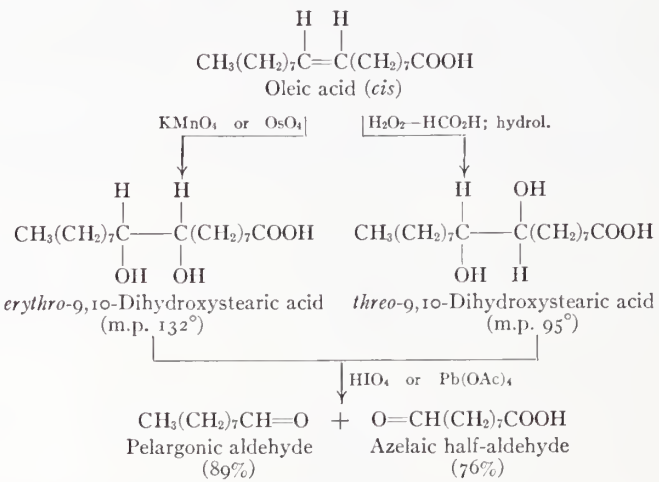
The biosynthesis of fatty acids is known to involve linking together of acetyl groups of acetic acid to form acetoacetic acid, CH_3COCH_2COOH, which then gives $CH_3COCH_2COCH_2COOH$, $CH_3COCH_2COCH_2COCH_2COOH$, and higher polyacetic acids. Carbonyl groups are then eliminated by reduction to the alcohol, dehydration, and hydrogenation. This pathway accounts for the fact that the natural acids all have straight chains with an even number of carbon atoms. Why double bonds are arranged as they are and why they are always *cis* is not yet understood.

17.13

Biosynthesis

17.14 Structure Determination. — The position of a double bond in an unsaturated acid usually is established by identification of the products formed on oxidative degradation. Oxidation of oleic acid with either a dilute solution of permanganate at 0° or with osmium tetroxide proceeds by *cis*-addition and gives one of two possible diols. Since these diols are related to each other in the same way that the tetroses erythrose and threose (16.15) are related, they are called the *erythro*-

cis-Hydroxylation



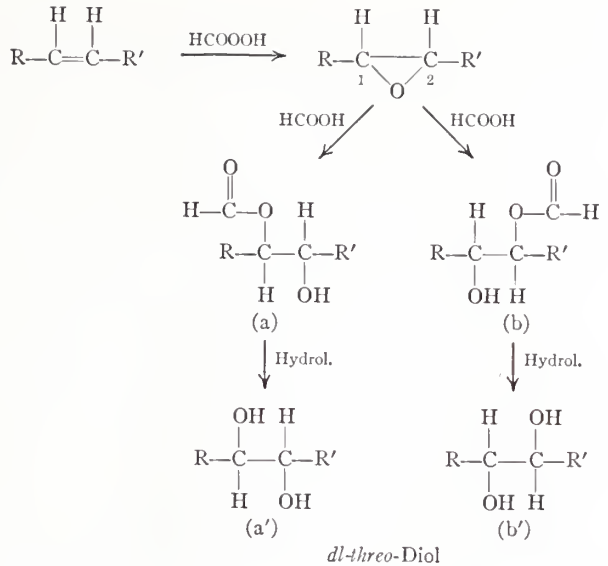
and the *threo*-diol. That resulting from *cis*-hydroxylation is the *erythro*-diol. Actually the formula represents the product of opening of one member of the double bond. Opening of the second member of the double bond occurs to an exactly equal extent to give a product with the two hydroxyls and hydrogens in the reversed positions. The *erythro*-diol formed is thus the optically inactive *dl*-mixture.

17.15 The *threo*-diol is also formulated for brevity as a single, optically active isomer, but the actual product is likewise the *dl*-form. Hydroxylation with hydrogen peroxide in formic acid solution, followed by hydrolysis, proceeds as follows. When hydrogen peroxide is dissolved in formic acid, performic acid is formed:

Reaction with H_2O_2 involves oxide formation

$$HCOOH + HOOH \longrightarrow HCOOOH + HOH$$

This peracid reacts with an ethylene by giving up its extra oxygen to form an oxide. The oxide is then cleaved by formic acid to produce an ester group on the carbon of the bond severed and a hydroxyl group at the second carbon atom. The attack by the reagent is from the back side and occurs with Walden inversion at the carbon of the bond severed. Thus cleavage of the bond from C_1 to oxygen involves Walden inversion at C_1 and gives (a), and cleavage of the bond to C_2 gives (b). The product of hydrolysis is then a mixture of equal parts of (a′) and (b′), that is, the *dl-threo*-diol. As shown in the



dl-threo-Diol

Oxide cleavage with inversion

formulation above, glycol cleavage of either the *erythro*- or the *threo*-diol with periodic acid gives the C_9-aldehyde (pelargonic) and the C_9-aldehyde-acid (azelaic) in excellent yields. Lead tetraacetate is an equally good reagent for effecting glycol cleavage.

Natural and Hydrogenated Fats. — The degree of unsaturation is 17.16
the most important factor in determining the physical as well as the chemical properties of both glycerides and fatty acids. Oleic acid is a liquid melting about 55° below the substance of which it is the 9,10-dehydro derivative, and melting points drop progressively on introduction of one and two more double bonds. Synthetic tristearin, that is, the tristearyl ester of glycerol, is a solid of melting point (71°) close to that of stearic acid (70°), whereas triolein, like oleic acid, is liquid at room temperature. Mixtures of glycerides do not show the usual melting point depressions but melt at temperatures intermediate between the melting points of the components. The animal fats tallow and lard are preferable to the more abundant and less expensive vegetable oils for manufacture of soap and for use in certain foods largely because they are solids (m.p. range 36–47°) rather than liquids, and the difference lies in the extent of unsaturation. The degree of unsaturation of a fat is measured by the iodine value, which is the number of grams of iodine that combine with one hundred grams of fat. Test solutions employ iodine monochloride (ICl), which is more reactive than iodine alone. Iodine values of samples of beef tallow are in the range 32–47; for peanut oil the range is 85–90, for whale oil it is 110–150.

Degree of unsaturation determines m.p.

Iodine value

The extent of unsaturation of fat may be markedly influenced 17.17

by the temperature at which biosynthesis occurs. Warm-blooded animals tend to produce solid fats that are fluid at, or only a little above, body temperature. Variation may occur in fats from different parts of the organism. Neat's-foot oil, from the hoofs of cattle, has a higher iodine number than fats derived from other locations. A gradation is noted in the subcutaneous fat of the pig, the outer layers of which are progressively unsaturated. The striking influence of climate on the composition of linseed oil is shown by the following comparison: an iodine value of 190 has been reported for linseed oil from seed grown in the cold climate of Switzerland, and a value of 93 for oil from seed of the same stock grown in a Berlin greenhouse at a temperature of 25–30°. The degree of unsaturation is also dependent on the type of fat in the diet. The iodine value of lard of corn-fed hogs is 69–72, of peanut-fed hogs, 90–100.

17.18 ——— Since the principal unsaturated acyl components of fats are convertible to stearyl groups by catalytic hydrogenation, unsaturation in a natural fat or oil can be reduced to any stage desired by hydrogenation (Ni catalyst). Since hydrogenation progressively raises the melting point, the process is described as hardening; abundant, highly unsaturated vegetable oils (peanut, cottonseed, soybean) are hardened by hydrogenation to more valuable products for use in making soap or to lard substitutes for use as cooking greases. Whale oil (iodine number 110–150) is partially hydrogenated to reduce the most highly reactive unsaturated centers and so eliminate odor and produce more stable oils for use as salad oil and in the compounding of cosmetics. Lard is often hydrogenated to improve keeping qualities, since development of rancidity is associated with unsaturation.

Hardening of fats

17.19 ——— **Drying Oils.** — Drying oils are mixed glycerides of highly unsaturated fatty acids and may be classified in two groups according to the nature of unsaturation. One group includes linseed oil (Argentina) and perilla oil (Japan). Both oils have iodine numbers in the range 170–210, and in both the major acid components, which together account for 85% of the total acids, are linoleic and linolenic acid, in which the double bonds are not conjugated but separated by methylene groups. A second group includes tung oil (China) and oiticica oil (Brazil). These have iodine values in the range 140–180 and are thus not so highly unsaturated as the first group, but the double bonds in the characteristic component acids are conjugated. The major acid of tung oil (80% of total acids) is eleostearic acid, an isomer of linolenic acid in which the usual 9,10-double bond is con-

Multiple nonconjugated double bonds

$$CH_3CH_2CH_2CH_2\overset{14}{C}H=\overset{13}{C}H\overset{12}{C}H=\overset{11}{C}H\overset{10}{C}H=\overset{9}{C}H(CH_2)_7COOH$$

Eleostearic acid (m.p. 49°)

jugated with the other two. In oiticica oil the major acid (74%) is licanic acid, the 4-keto derivative of eleostearic acid.

Conjugated triene systems

$$CH_3CH_2CH_2CH_2\overset{14}{C}H{=}\overset{13}{C}H\overset{12}{C}H{=}\overset{11}{C}H\overset{10}{C}H{=}\overset{9}{C}HCH_2CH_2CH_2CH_2\overset{4}{C}OCH_2CH_2COOH$$

Licanic acid (m.p. 75°)

The four oils named possess the ability, when spread on a surface and exposed to air, to slowly form dry, tough, and durable films. Mixtures with insoluble pigments are used as paints; varnishes are mixtures of drying oils with resins. The drying of these oils is not dependent upon evaporation of a solvent, as with modified nitrocellulose lacquers (19.11), but involves oxidative polymerization. Although the nature of the reactions remains to be clarified, the process appears to be initiated by reaction with molecular oxygen to form a hydroperoxide. In linoleic and linolenic acid residues, a methylene group flanked by two activating double bonds (a) presents a point of vulnerability to attack by oxygen to give either the corresponding

17.20

Mechanism of drying

$$-CH{=}CHCHCH{=}CH- \xleftarrow{O_2} -CH{=}CHCH_2CH{=}CH- \xrightarrow{O_2}$$

OOH
(b)

(a)

$$-CH{=}CHCH{=}CHCH-$$

OOH
(c)

hydroperoxide (b) or, more probably, that (c) resulting from an allylic shift in the course of the reaction with formation of a conjugated system. In eleostearic and licanic acid the methylene groups adjacent to the two ends of the conjugated triene system appear to be more highly activated and hence more vulnerable to oxidation, for tung and oiticica oil dry more rapidly than linseed and perilla oil and are generally superior to these oils. Raw linseed oil dries only slowly, but the performance is improved by boiling the oil with lead oxide. Boiled linseed oil contains suspended lead salts which give it a muddy appearance, and modern boiled oils are made by incorporation into the oil at a more moderate temperature of a metal-containing oxidation catalyst, or drier, such as the cobalt or manganese soap (salt) of naphthenic acid (8.3). Oilcloth is made by applying several coats of linseed-oil paint to a woven canvas; linoleum is made by cementing cork particles with thickened linseed oil and rosin.

Hydraperaxides

Drier = oxidatian catalyst

Soaps. — Natural or hardened fats are saponified with a solution of sodium hydroxide in an open kettle having at the bottom closed coils for indirect heating and perforated coils for direct heating through which steam can be passed at a rate to maintain agitation and ebullition. When the reaction is complete, salt is added to pre-

17.21

cipitate thick curds of the soap (common-ion effect). The aqueous layer containing glycerol is drawn off and concentrated to glycerol, which is refined by distillation in vacuum. The crude curds contain glycerol, alkali, and salt; the impurities are removed by boiling with sufficient water to form a homogeneous liquid, followed by reprecipitation of the soap with salt. In this way the soap is given several washings for recovery of glycerol and removal of impurities; then it is boiled with sufficient water to give a smooth mixture, which on standing separates into a homogeneous upper layer of kettle soap.

Manufacture of kettle soap

Kettle soap contains 69–70% soap, 0.2–0.5% salt, and about 30% water; some is sold as such or after addition of perfume or dye for household purposes. Sand, sodium carbonate, and inert fillers are added for scouring soaps; cresol or other antiseptic for medicated soaps. Powdered soaps are prepared by mixing kettle soap with builders or alkaline detergents (sodium silicate, sodium carbonate) and with an emulsifying agent (tetrasodium pyrophosphate); the hot mixture is then spray-dried. Toilet soaps are made from kettle soap dried to a content of 85–90% and milled with perfume to thin shavings, which are then compacted in bars that are cut and pressed into cakes; transparent soaps are made by dissolving partly dried soap in alcohol. The specific gravity of ordinary soap is about 1.05,

Floating soap

but by blowing air into hot molten kettle soap the specific gravity can be lowered to 0.8–0.9 (floating soap).

17.22

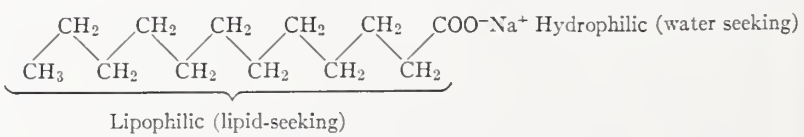
Tallow (depot fat of cattle and sheep) is the most important soap stock. Soap made from tallow alone has excellent detergent and water-softening properties but must be used in hot water (tallow yields mainly C_{16}- and C_{18}-acids, whose soaps are only slightly soluble in water). The nut oils, coconut, babassu, and palm kernel oil, are

Preferred fats

widely used in conjunction with tallow; their value lies in the high content of C_{12}- and C_{14}-acids, the soaps of which are firm and also readily soluble. Very unsaturated components cannot be used for soap since they are subject to oxidation.

17.23

Detergency. — The detergency, or cleansing power, of soap is dependent in part upon a striking lowering in surface tension. The surface tension of pure water is 73 dynes/cm.; that of solutions of sodium oleate or linoleate is about 25 dynes/cm. Another factor contributing to the surface activity of a substance such as sodium laurate is that it has a large, lipophilic hydrocarbon part balancing a



Sodium laurate ($C_{11}H_{23}COO^-Na^+$)

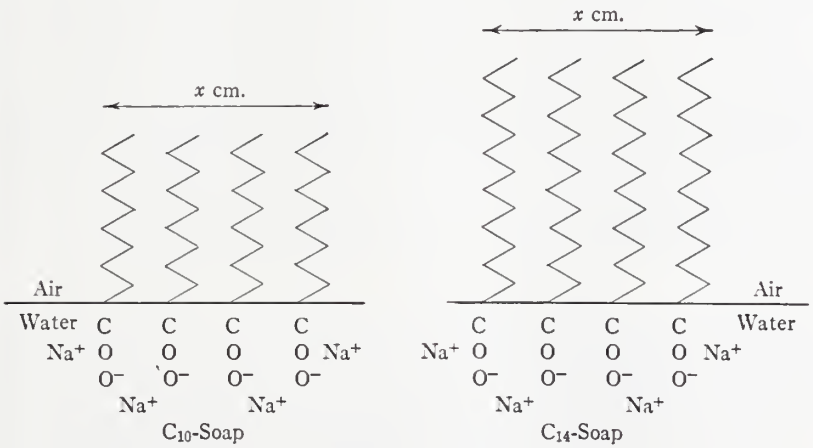
Lipophilic-hydrophilic balance

polar hydrophilic group; the latter group though small is potent, since it is ionic. The balance is at a maximum in the C_{12}-laurate. Soaps of lower acids are too predominantly hydrophilic; detergent efficiency decreases as the chain is lengthened and disappears with the C_{22}-soap, which is practically insoluble in water.

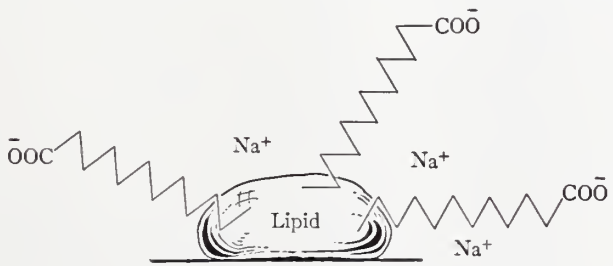
17.24

Irving Langmuir, at the General Electric laboratories (1916), showed that a drop of fatty acid oil when placed on a clean surface of sodium hydroxide solution spreads rapidly until it covers a definite area, when it spreads no farther. A surface film is formed in which the $-COO^-Na^+$ group is dipping in the water and the hydrocarbon part is directed away from the water. The film is only one molecule

Langmuir films



deep and, because of the orientation, equivalent weights of homologous acids spread to films of the same area, as illustrated diagrammatically for a C_{10}- and a C_{14}-soap. Removal of oil, grease, or a solid lipid particle can be pictured as involving merging of the hydrocarbon



Emulsion

part of the soap with the lipid spot or particle so that this is supplied with a number of hydrophilic groups and thereby detached from the fiber and dispersed in the aqueous phase as an emulsion. Particles are kept from coalescing by a protective film of soap, functioning as the emulsifier.

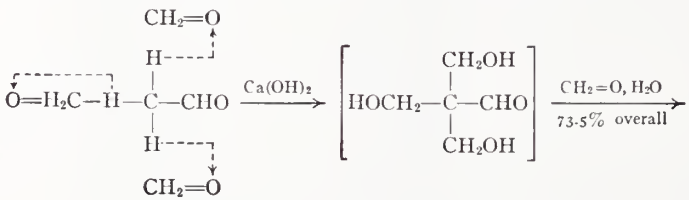
17.25 **Synthetic Surface-active Agents.** Surface-active compounds, including substances of value as detergents, wetting agents, and emulsifiers, are manufactured in a variety of types. Each has a lipophilic part, usually a fairly large hydrocarbon residue, and a hydrophilic functional group to provide distribution into the aqueous phase of a water-oil mixture. The latter function is usually an ionic group of fixed character, and the proper lipophilic-hydrophilic balance is attained by adjustment of the size of the hydrocarbon part. Since the field is highly competitive, the price of commercial products is kept at a minimum by use of fatty acid mixtures from fats and of alkane mixtures from petroleum, and actually mixtures probably function better than pure individual components because of coemulsifying action. Detergents of one type are made by hydrogenolysis of fat to a mixture of alcohols, which is converted into a mixture of sodium sulfate esters; the nut oils give superior detergents because of the high content of the C_{12}-sulfate I, derived from lauric acid. Being



salts of strong acids, the sodium sulfate esters are more stable than soap in solutions of low pH.

17.26 Surface-active agents of another type are exemplified by a mixture of which the chief component is monostearoyl pentaerythritol, II; here the hydrophilic function is not ionic but is a triol grouping. Pentaerythritol is made by an interesting process in which the first step is an aldol condensation of acetaldehyde with three molecules of formaldehyde. The resulting aldehyde, shown in brackets, is then

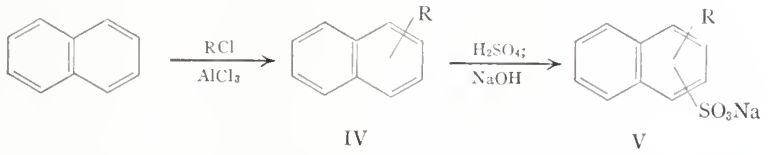
Reduction by the Cannizzaro reaction



reduced at the expense of formaldehyde, which becomes oxidized to formic acid; this oxidation-reduction reaction is named for an early Italian chemist who discovered it, Stanislao Cannizzaro.

Surface-active agents of two types utilize the sodium sulfonate group, $-SO_3Na$, for distribution into the aqueous phase. In one, the alkane mixture (RH) of a petroleum fraction of appropriate molecular weight is converted by reaction with sulfur dioxide and chlorine into the sulfonyl chloride derivative and this is saponified to the sodium sulfonate (III). In the other, a petroleum fraction is chlorinated to an alkyl chloride mixture, RCl, and this is condensed with an aromatic

$$RH \xrightarrow{SO_2,\ Cl_2} RSO_2Cl \xrightarrow{NaOH} \underset{III}{RSO_3Na}$$



IV V

hydrocarbon such as naphthalene under catalysis from aluminum chloride (Friedel-Crafts reaction) to produce a mixture of isomers and homologs roughly represented by formula IV. Sulfonation and conversion to the sodium sulfonates gives a surface-active preparation V.

SUMMARY

Term lipid designates water-insoluble, oil-soluble plant or animal product. Neutral fats are mixed glycerides, e.g., of stearic (C_{18}) and palmitic (C_{16}) acid; saponification (alkaline hydrolysis) gives soap + glycerol. Lecithin, a phospholipid, saponified to glycerol, fatty acids, phosphate, and choline.

Nonsaponifiable lipids. (*a*) Steroids. Cholesterol (C_{27}, one β-OH, one double bond), abundant constituent of animal tissues. Bile acids, e.g. cholic acid (C_{24}, three α-OH). Present in bile conjugated with glycine as sodium salt. Function of bile salts: to emulsify neutral fats and promote absorption.

(*b*) Steroid hormones. Sex hormones: testosterone (C_{19}), estradiol (C_{18}), and progesterone (C_{21}). Adrenal cortical hormone: cortisone (C_{21}). Isolated from very large amounts of glandular tissue or urine.

(*c*) Vitamin D_3 from cod liver oil.

(*d*) Isoprenoid types. Squalene (shark liver oil): C_{30}, six isoprene units linked t—h, t—h, t—t, h—t, h—t. Vitamin A (fish oils): C_{20}, four isoprene units, a primary allylic alcohol. Tocopherol (wheat germ oil, liver): trimethylhydroquinone + phytol, a C_{20}-alcohol from chlorophyll. Vitamin K_1 (alfalfa): a quinone with a phytyl chain.

Glyceride Fats and Oils

Fatty acid components: all straight-chain, even number of carbons. Saturated: lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}), stearic (C_{18}). Unsaturated (all hydrogenable to stearic, all *cis*): oleic (double bond at center), linoleic and linolenic (2 and 3 nonconjugated double bonds). Structure of oleic acid established by oxidation to *erythro*-diol (*cis*-addition) or *threo*-diol (through the oxide, cleaved with Walden inversion); both diols on glycol cleavage yield a C_9-aldehyde and a C_9-aldehyde-acid.

Natural fats. M.p. determined by degree of unsaturation, measured by iodine value. Cheap vegetable and whale oils converted to more valuable solid fats or more saturated oils by hydrogenation (hardening).

Drying oils. Linseed and perilla oil rich in linoleic and linolenic acid (multiple nonconjugated double bonds). Superior oils: tung and oiticica, rich in eleostearic acid (conjugated triene system) or its 4-keto derivative licanic acid. Drying involves oxidative polymerization initiated by allylic air oxidation to a hydroperoxide. Linseed oil improved by boiling with lead oxide or incorpora-

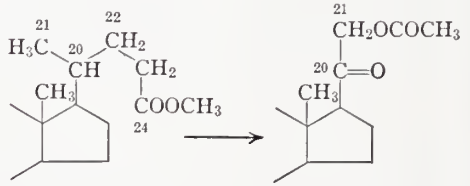
tion of cobalt or manganese naphthenate as drier (oxidation catalyst).

Soaps. Method of production of sodium soaps; recovery of glycerol. C_{12}–C_{14} acids of nut oils improve quality (better water-solubility). Detergency dependent upon reduction of surface tension and orientation at oil-water interface; Langmuir films.

Synthetic surface-active compounds. Combination of a lipophilic hydrocarbon group (C_{12}–C_{14}) with a hydrophilic group ($—OSO_3^-Na^+$, $—SO_3^-Na^+$, several OH groups). Pentaerythritol by aldol addition of 3 $CH_2{=}O$ to $CH_3CH{=}O$, with reduction of the product by $CH_2{=}O$ (Cannizzaro reaction).

PROBLEMS

1. How many asymmetric carbon atoms are there in (*a*) cholesterol and in (*b*) cholic acid, and how many stereoisomeric forms are possible in each case (see 15.20)?
2. How could you separate estradiol from a mixture of this hormone with testosterone, progesterone, and cortisone?
3. By what technique or physical measurement should it be possible to detect the presence of vitamin D_3 in a sample of cholesterol?
4. Cite an analytical method by which the number of hydroxyl groups in cortisone could be determined.
5. What product would you expect to result from treatment of cyclohexene with hydrogen peroxide in formic acid solution, followed by hydrolysis?
6. Suppose a paint manufacturer suspected a sample of drying oil purchased as authentic tung oil of being, in fact, merely linseed oil diluted with a cheap oil (peanut, whale) to give the correct iodine number. How could the matter be settled?
7. Cortisone, required for the treatment of rheumatoid arthritis, is available by isolation in only minute amounts, for example, 340 mg. from 1000 lbs. of hog adrenal glands. Synthetic methods, although lengthy, are thus employed in the pharmaceutical industry for manufacture of the hormone. The first-introduced process is a thirty-two step synthesis starting with cholic acid from ox bile. A part of the synthesis involves a degradation represented with partial formulas as the conversion of I into II. See



I II

if you can formulate the degradation from the following description of the steps: (*a*) reaction with 2 C_6H_5MgBr; (*b*) dehydration; (*c*) reaction with N-bromosuccinimide (NBS); (*d*) dehydrobromination; (*e*) reaction with NBS; (*f*) reaction with potassium acetate; (*g*) oxidation.

CHAPTER 18

PROTEINS

18.1

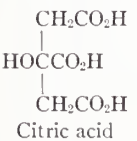
Proteins (Gr. *proteios*, primary) derive their name from their great importance in all living tissues. Proteins differ from carbohydrates and fats in elementary composition, for in addition to carbon, hydrogen, and oxygen, they invariably contain nitrogen (16–18%) and usually sulfur. Proteins of one type, the fibrous proteins, are insoluble in water and serve as structural materials for animals much as cellulose serves for plants. Fibroin, the protein of silk, is an example. Others are collagen, the protein of connective tissue (tendons, ligaments), which yields gelatin when boiled with water; keratin, the protein of epithelial tissue, of hair, wool, horn, feathers, nails; elastin, the protein of elastic connective tissue. A second broad group is that of the globular proteins, characterized by solubility in water or in aqueous solutions of acids, bases, or salts. Examples are egg albumin (white of egg), casein (from milk), and proteins of blood plasma and of red blood corpuscles.

Fibrous proteins (water-insoluble)

Globular proteins (soluble)

18.2

Blood for chemical or biochemical investigation is usually drawn from a horse, and clotting can be prevented by immediate addition of a solution of sodium citrate. A preparation from liver containing the polysaccharide heparin also prevents clotting. Centrifugation of the clot-free blood causes settling of the heavier red blood corpuscles and separation of a yellowish, opalescent supernatant liquid that constitutes blood plasma and is an approximately 7% solution of plasma proteins in water at a pH close to 7.0. If the plasma is siphoned off and the sludge of corpuscles stirred with a little ether, the ether reduces the surface tension of the liquid external to the cells but does not penetrate the cell membranes and hence does not alter the pressure within the cells; the result is that the cells burst. A further centrifugation causes the ruptured cell membranes to settle and gives a



Citric acid

Blood plasma

rich red solution of the globular protein hemoglobin. This is the protein responsible for transportation of oxygen from the lungs to all body tissues. The mechanism of animal respiration can be demonstrated with the solution of hemoglobin prepared as described: when the solution is shaken with oxygen it becomes bright red (arterial blood), and when it is evacuated at the suction pump it becomes bluish red (venous blood). Hemoglobin is an example of a conjugated protein, and it contrasts with the above-mentioned substances, which are simple proteins. Hemoglobin is a conjugate of a protein proper, globin, and a much smaller nonproteinic C_{34}-component, heme. The component heme that is attached to the protein is known as a prosthetic group (Gr. *prosthetos*, put on). Actually heme, which contains iron, is responsible for the red color of blood and is essential for its function as oxygen carrier.

Hemoglobin = heme conjugated with globin

18.3

Blood plasma, prepared by the procedure described, contains the following globular proteins: albumins, globulins (insoluble in pure water but soluble in 5% salt solution), lipoproteins (containing up to 75% lipids), fibrinogen, and prothrombin. Whole blood that is not protected with citrate or heparin as it is drawn clots on standing for a few minutes as the result of conversion of the soluble fibrinogen, under the influence of prothrombin, into an insoluble, fibrous protein fibrin, strands of which form the enmeshing structure of the clot. Centrifugation of clotted blood gives a residual mixture of fibrin and red blood corpuscles and a supernatant solution known as blood serum. Serum differs from plasma in that it contains no fibrinogen.

Blood serum

18.4

Proteins consist of giant molecules of molecular weights ranging from about 12,000 to several million units. Those proteins that are soluble in water form colloidal solutions. Chemical characterization is limited by the extreme sensitivity of the substances; treatment with an acid, a base, or an organic solvent is liable to produce a fundamental change described as denaturation, which is attended with loss of originally characteristic properties, such as water solubility or specific biological activity. Mild heating usually results in denaturation with loss in solubility, as illustrated by the familiar phenomenon of the change induced by hot water on egg white. As in most instances, the denaturation of egg albumin is irreversible.

Denaturation of proteins

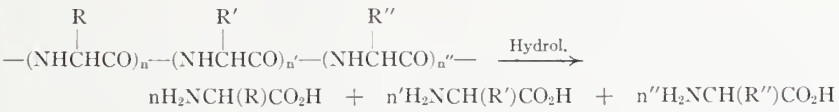
18.5

All proteins can be hydrolyzed by aqueous solutions of mineral acids at the boiling point, and they all afford mixtures of α-amino acids of the type $RCH(NH_2)CO_2H$. Analytical evidence shows that the carboxyl and α-amino groups represented in the type formula are not present as such in the protein but that they are liberated in equal amounts on hydrolysis. Thus the building units are joined together through the link —CO·NH— between the carboxyl group

Hydrolysis to amino acids

of one amino acid and the amino group of another. This particular type of amide group is called a peptide link, and proteins are described as polypeptides. The process of protein hydrolysis can be represented in part as the cleavage of a polypeptide chain:

Polypeptide structure



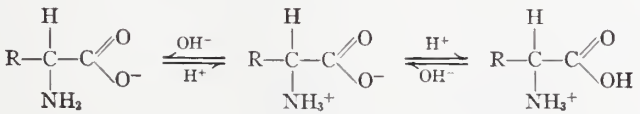
AMINO ACIDS

Component Acids of Proteins. — Glycine, $H_2NCH_2CO_2H$, the simplest amino acid derived from proteins, was the first component to be discovered. Braconnot (1820), investigating the hydrolysis of gelatin to see if this material, like cellulose, would yield a sugar, isolated a substance which he called glycine because it had a sweet taste (Gr. *glykys*, sweet), and eighteen years elapsed before the supposed "sugar of gelatin" was found to contain nitrogen. Subsequent investigations of protein hydrolyzates have led to recognition of twenty acid components of established structure. All known components are α-amino acids, and with the sole exception of glycine the α-carbon atom is asymmetric. Thus one group includes the following homologs: alanine, $CH_3CH(NH_2)CO_2H$; valine, $(CH_3)_2CHCH(NH_2)CO_2H$; leucine, $(CH_3)_2CHCH_2CH(NH_2)CO_2H$. Valine is the isopropyl homolog of alanine and leucine is the isobutyl homolog, and most of the other component acids are alanine derivatives: $RCH_2CH(NH_2)CO_2H$. — 18.6

Type $RCHCO_2H$ (with NH_2)

These substances are neutral amino acids, since each contains the same number of amino and carboxyl groups. They are amphoteric and at suitable pH can ionize as either acids or bases. The pH at which acidic ionization balances basic ionization is called the isoelectric point; for neutral amino acids the values range from 4.8 to 6.3. The electrically neutral form predominating at the isoelectric point is a dipolar ion carrying both a positive and a negative charge. The ionic — 18.7

Isoelectric point



Dipolar ion

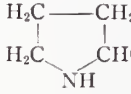
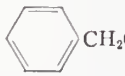
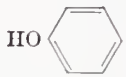
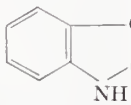
Inner salt structure

structure explains the fact that the acids are relatively infusible and nonvolatile.

The list of common amino acids given in Table 18.8 includes conventional symbols and isoelectric points. The first five members of the neutral group differ in the size and structure of the alkyl side chain, $RCH(NH_2)CO_2H$. Proline can be regarded as a cyclized — 18.8

TABLE 18.8

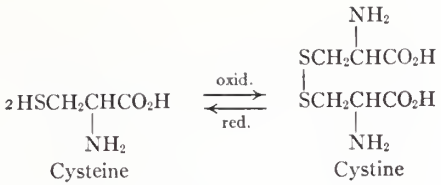
AMINO ACIDS FROM PROTEINS

Name	Symbol	Formula	Isoelectric point
A. Neutral Amino Acids			
Glycine	Gly	$CH_2(NH_2)COOH$	5.97
Alanine	Ala	$CH_3CH(NH_2)COOH$	6.00
Valine	Val	$(CH_3)_2CHCH(NH_2)COOH$	5.96
Leucine	Leu	$(CH_3)_2CHCH_2CH(NH_2)COOH$	6.02
Isoleucine	Ileu	$CH_3CH_2CH(CH_3)CH(NH_2)COOH$	5.98
Proline (*Pyrrolidine ring*)	Pro		6.30
Phenylalanine	Phe		5.48
Tyrosine	Tyr		5.66
Tryptophan (*Indole system = benzene ring fused to a pyrrole ring*)	Try		5.89
Cysteine	CySH	$HSCH_2CH(NH_2)COOH$	5.05
Cystine	CyS·SCy	$[—SCH_2CH(NH_2)COOH]_2$	4.8
Methionine	Met	$CH_3SCH_2CH_2CH(NH_2)COOH$	5.74
Serine	Ser	$HOCH_2CH(NH_2)COOH$	5.68
Threonine	Thre	$CH_3CH(OH)CH(NH_2)COOH$	
B. Acidic Amino Acids			
Aspartic acid	Asp	$HOOCCH_2CH(NH_2)COOH$	2.77
Glutamic acid	Glu	$HOOC(CH_2)_2CH(NH_2)COOH$	3.22
C. Basic Amino Acids			
Lysine	Lys	$NH_2(CH_2)_4CH(NH_2)COOH$	9.74
Arginine (*Guanidyl group = $H_2NCNH—$ with NH above the C*)	Arg	$NH_2C(=NH)NH(CH_2)_3CH(NH_2)COOH$	10.76

n-alkyl-α-amino acid. In phenylalanine, $C_6H_5CH_2CH(NH_2)COOH$, a phenyl group is joined to an alanyl residue; tyrosine is the *p*-hydroxy derivative of phenylalanine. Tryptophan is similar except that the aromatic group attached to an alanyl residue is the bicyclic indole group, which contains a five-membered, nitrogen-containing pyrrole ring fused to a benzene ring.

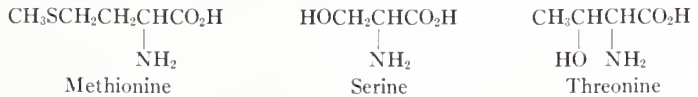
18.9 Cysteine is the β-thiol or β-sulfhydryl derivative of alanine. It is readily oxidized to the disulfide cystine, which can be reconverted into cysteine by reduction. Methionine contains the thiomethyl group (CH_3S); it is derived not from cysteine but from the next higher homolog, homocysteine, which itself is not a protein component.

Sulfur-containing acids



Serine is the oxygen analog of cysteine, and threonine is the β-methyl homolog of serine; threonine contains two asymmetric carbon atoms.

Hydroxyamino acids



Aspartic and glutamic acid are acidic, since they contain a second carboxyl group not paired with a basic function; the isoelectric values

18.10

Acidic types



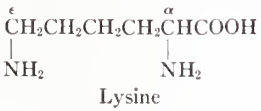
are 2.8 and 3.2, respectively. These amino derivatives of succinic and glutaric acid occur in proteins to some extent as the monoamides, asparagine and glutamine:



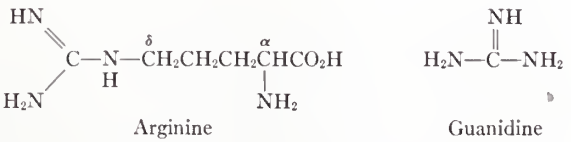
Acids of a third type, illustrated by lysine, contain two amino groups and only one carboxyl group and are basic (isoelectric point

18.11

Basic types



9.7). A second important basic amino acid is arginine, the δ-guanidyl derivative of α-aminovaleric acid; guanidine is the imide of urea and is very strongly basic. The guanidyl group renders arginine the most basic protein component (isoelectric point 10.8).



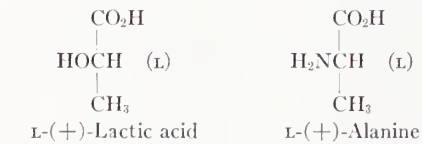
Solubilities. — The solubility of a polypeptide or protein is determined by the solubility characteristics of the component amino acids. Among the neutral amino acids of the type $RCH(NH_2)CO_2H$, solubility in water decreases with increasing size of the R group, as can be seen from the following figures for grams of acid dissolved by

18.12

100 g. of water (25°): glycine, R = H, 25.0; alanine, R = CH_3, 16.7; valine, R = $CH(CH_3)_2$, 8.8; leucine, R = $CH_2CH(CH_3)_2$, 2.4. Conversely, solubility in organic solvents (lipophilic character) increases with increasing size of the hydrocarbon side chain. Thus a mixture of glycine and leucine can be separated by repeated extraction with hot butanol, which dissolves only the more lipophilic leucine. Hydroxyl groups (Ser, Thre), sulfhydryl groups (CySH), carboxyl groups (Asp, Glu), and amino groups (Lys) are water-seeking and increase hydrophilic character.

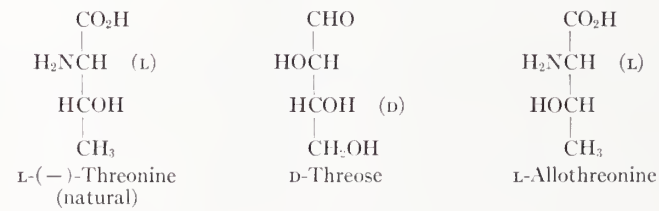
18.13 Configuration. — The α-carbon atom of all the amino acids except glycine is asymmetric, and it is noteworthy that all the natural acids derived from proteins have the same configuration at this center, regardless of the sign of rotation. Natural alanine has been related to L-(+)-lactic acid, and hence all the acids from proteins belong to the L-series; since natural alanine is dextrorotatory, it is fully described as L-(+)-alanine. A natural amino acid that contains a second

Natural acids are of the L-series



center of asymmetry is designated L to indicate the correspondence in the configuration of the α-carbon atom with that of L-alanine, and the enantiomer is designated D. The diastereoisomers of these substances are designated by the prefixes L-allo and D-allo, the letter denoting the configuration of the α-carbon atom; for example natural threonine was so named because of its relationship to D-threose; in the amino acid the prefix L- refers to the configuration of the α-carbon

Correlation of threonine



atom, whereas in the carbohydrate the prefix D- refers to the carbon atom β to the aldehyde function.

18.14 Isolation of Amino Acids. — For hydrolysis of a protein with the object of isolating component acids, the material is usually refluxed with hydrochloric acid (20%) or sulfuric acid (35%). Hydrolysis with hot alkali is less useful because it leads to extensive racemization of most of the products. Enzymatic hydrolysis is sometimes employed because it is less destructive to sensitive amino acids, but the reaction is slow and never complete.

All proteins afford hydrolyzates that are complex mixtures of some ten to eighteen individual amino acids and separation obviously is difficult. Because they are dipolar, saltlike, amino acids are not distillable. However, Emil Fischer introduced in 1901 the technique of esterification of a protein hydrolyzate and fractional distillation of mixtures of esters of the type $RCH(NH_2)CO_2CH_3$ derived from the neutral amino acids present. Since the component acids have rather low molecular weights, the increment of 14 units between homologs produces a fair spread in boiling point adequate for separation. The technique of ester distillation led to the discovery of valine, proline, and γ-hydroxyproline. Selective precipitation reactions have also been useful. For example, tryptophan was first isolated from a hydrolyzate by precipitation with mercuric sulfate, and arginine by precipitation with phosphotungstic acid. The latter reagent is specific for the basic amino acids and precipitates both arginine and lysine, if present.

18.15

Ester-distillation

Precipitation methods

Synthesis of Amino Acids. — Methods of synthesis, apart from initial interest for completion of evidence of structure, have been investigated extensively with the object of making acids available where required as dietary supplements; poultry feed, for example, is enriched in lysine. Although the initial product of a synthesis is a racemic mixture, resolution usually can be accomplished without difficulty. A general method consists in selective enzymatic hydrolysis of the L-form of a DL-acetylamino acid (15.25). Currently, some of the amino acids are still more readily available by isolation than by synthesis. Two of many known synthetic methods are illustrated.

18.16

One route to α-amino derivatives of available acids consists in introduction of an α-chloro or α-bromo substituent by catalyzed halogenation and amination of the halo acid with a large excess of ammonia. The preparation of DL-alanine by this method has been described (9.13). The Strecker synthesis combines the addition of hydrogen cyanide to an aldehyde and the condensation of the addition product with ammonia. When hydrogen cyanide is added to the carbonyl group of an aldehyde in the presence of ammonia, the latter reagent acts on the initially formed cyanohydrin with replacement of the hydroxyl by an amino group and formation of an aminonitrile, which affords an amino acid on hydrolysis.

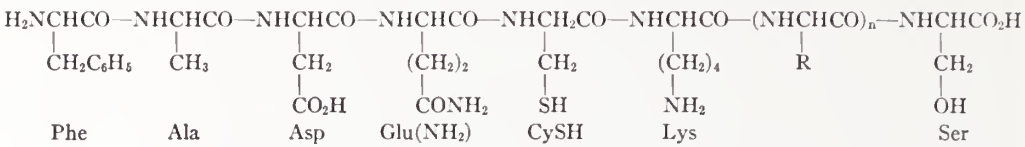
18.17

By amination

$$\underset{\text{Acetaldehyde}}{CH_3CHO} \xrightarrow{NH_3,\ HCN} \underset{\text{Aminonitrile}}{CH_3CHC{\equiv}N} \xrightarrow{2\ H_2O} \underset{\text{Alanine}}{CH_3CHCOOH}$$

NH_2 NH_2

Strecker synthesis



18.18 The hypothetical protein formulated has phenylalanine as the amino-terminal unit, conventionally written to the left, and serine as the carboxyl-terminal unit. The substance is amphoteric and substantially neutral, since it contains two basic groups (terminal $—NH_2$ and ϵ-NH_2 of Lys) and two acidic groups (terminal $—CO_2H$, and Asp-CO_2H). The sulfhydryl group (CySH) confers reducing properties, and the groups —SH, —OH, —COOH, and $—NH_2$ tend to promote water-solubility, whereas the hydrocarbon chains of Phe and Ala have the opposite effect. In the diacids (Asp, Glu), the α-carboxyl group is utilized for formation of the peptide link, and in units having two basic functions (Lys, Arg) the α-amino function is the one so utilized.

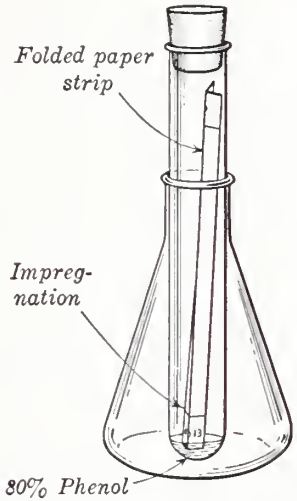
18.19 **Isolation and Purification.** — Most proteins are extremely prone to undergo irreversible alteration, or denaturation, and hence isolation of homogeneous individual components of protein mixtures in native form presents considerable difficulty. Since the solubility is at a minimum at the isoelectric point, adjustment of the pH to a particular value may favor separation of one component and retention of others when either a salt or a solvent such as ethanol is added in controlled amount to decrease the solubility. A method favored for slow addition of ammonium sulfate for isoelectric salting out of a protein is to rotate a cellophane bag of solid ammonium sulfate in the buffered protein solution; the electrolyte diffuses through the membrane and eventually causes precipitation of protein. If the precipitate, consisting of protein contaminated with the salt, is put in a bag and dialyzed against distilled water the ammonium sulfate is eliminated and the protein dissolves and can then be reprecipitated as before. Crystallization of proteins has been effected by suitable repetition of the process.

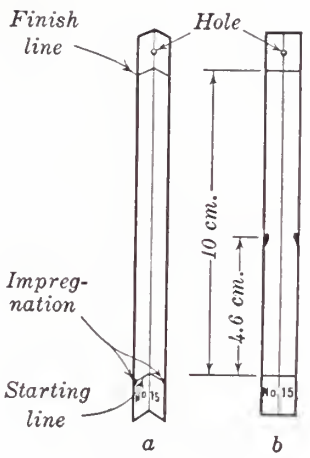
Isoelectric precipitation

18.20 **Amino Acid Analysis.** — Early data on the nature and proportion of the amino acid components of different proteins based upon yields of materials isolated by techniques of extraction, precipitation, and distillation have been supplemented by new techniques for assay of hydrolyzates. One, the method of paper strip chromatography, won recognition by the award of the Nobel Prize for 1952 to the British discoverers, A. J. P. Martin and R. L. M. Synge. Filter paper consists of cellulose containing about 22% of adsorbed water. When a

Paper strip chromatography

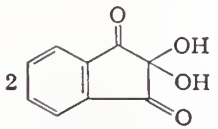
folded strip of paper is inserted into a test tube with the lower end dipping into phenol (1) the phenol ascends the strip by capillary flow





Partition between water (adsorbed on the paper) and phenol (ascends the strip)

without disturbance of the adsorbed water. The water thus forms a stationary phase and the organic solvent, phenol, a lipophilic moving phase. Before the folded strip is inserted, the paper is impregnated with tiny drops of an amino acid solution placed at the two ends of the starting line (2a). As the phenol rises on the strip the amino acids are subjected to innumerable partitions between the moving lipid phase and the stationary water phase. A highly lipophilic amino acid [e.g. $(CH_3)_2CHCH_2CH(NH_2)CO_2H$] travels almost as fast as the organic solvent, whereas a highly hydrophilic one [e.g. $HOCH_2CH(NH_2)CO_2H$] is largely retained by the water and makes little progress. In about two hours the solvent front reaches the finish line, 10 cm. from the starting line, and the strip is then removed, rinsed with acetone, and hung up to dry. The strip bears no indication of the position of an amino acid until it is sprayed with ninhydrin, which reacts with the amino acid to form a pigment. A spot then



Ninhydrin

appears at each edge of the strip, as shown in drawing 2b. The position of the front (top) of the spot is noted and its distance from the finish line measured with a ruler. The rate of flow, or Rf value, of a particular amino acid is the ratio of the distance traveled by the

Rf value

acid to the distance traveled by the solvent. In the example (2b), Rf = 4.6/10 = 0.46. Rf values range from that of cystine (0.16) to that of proline (0.85), and serve admirably for identification.

18.21 *Microbiological method*

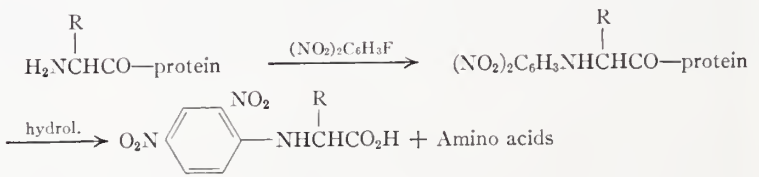
Another method of quantitative analysis is microbiological assay. A given microorganism requires certain amino acids for growth, and the rate of growth in a medium containing all but one essential acid provides an index of the amount of that component present in a test sample. Thus arginine in a hydrolyzate can be determined by the effect on growth of *Lactobacillus casei;* the concentration is determined by comparison with the effect of a standard sample at various concentrations.

18.22 *Isotope dilution method*

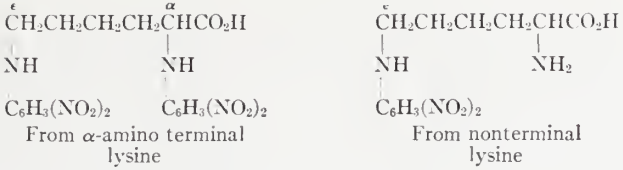
The isotope dilution method is theoretically applicable to any amino acid. A labeled acid of known isotopic content, for example isotopic glutamic acid, is added in known amount to the mixture to be analyzed, and glutamic acid is then isolated by the usual procedure. Since the chemical properties of the natural acid and the labeled acid are the same, the isolated material is a representative sample of added acid and acid originally present; the percent recovery is thus unimportant. The amount of acid in the hydrolyzate is calculated from the isotopic analysis of the isolated acid. The degree of accuracy is independent of the method of isolation, the yield, and the concentration in the hydrolyzate.

18.23 *End-group analysis*

Amino Acid Sequence. — When a protein has been isolated in a state of demonstrated purity, its molecular weight established, and the percentages of the component amino acids determined, the problem arises as to the sequence of amino acids in the polypeptide chain. F. Sanger, at Cambridge University, England, introduced in 1945 a method for identification of the amino acid unit at one end of the chain, namely that having a free α-amino group (conventionally written to the left). This amino group reacts with 2,4-dinitrofluorobenzene, $FC_6H_3(NO_2)_2$, to form a labeled unit, and on acid hydrolysis



the terminal unit is liberated as its bright yellow 2,4-dinitrophenyl derivative, which by paper chromatography is easily separated from the accompanying unlabeled amino acids and identified. Nonterminal lysine units are attacked but are recognizable from the fact that the derivative produced on hydrolysis has only one 2,4-dinitrophenyl group and not two.

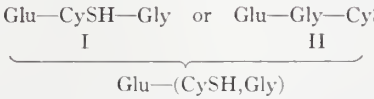


18.24

Glutathione, a tripeptide

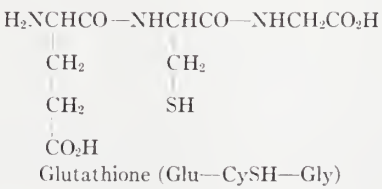
Glutathione, a tripeptide which occurs in nearly all living cells, yields on hydrolysis the acids glycine (Gly), cysteine (CySH), and glutamic acid (Glu). An abbreviated summary of this much information is given by the expression Gly,CySH,Glu or CySH,Glu,Gly, where the commas indicate that no particular sequence of the units is implied. Actually Sanger end-group analysis reveals glutamic acid as the amino-terminal group, and this additional information is expressed by replacing one comma by a connecting dash: Glu—. Glutathione is therefore either I or II. A decision can be reached by

Determination of amino acid sequence



partial hydrolysis of glutathione sufficient to give a mixture containing dipeptides, along with unchanged tripeptide, and with amino acids resulting from complete hydrolysis. Two dipeptides are possible, but perhaps only one can be isolated. If this is found on hydrolysis to be made up of CySH and Gly, the problem of sequence is still unsolved but can be settled by Sanger end-group analysis of the dipeptide. This analysis shows CySH to be the amino-terminal unit, and hence the dipeptide is CySH—Gly. Since Glu is known to be amino-terminal, or to the left, in the tripeptide, glutathione must be Glu—CySH—Gly.

The conclusion

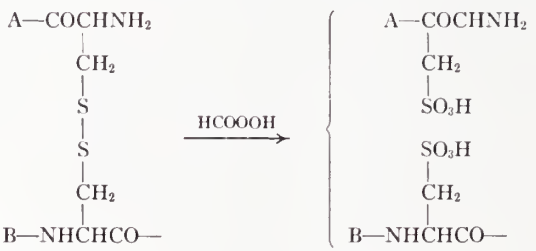


18.25

The same conclusion would be reached without the second end-group analysis if two dipeptides could be isolated. Hydrolysis and identification of the component acids would show the two dipeptides to be Glu,CySH and CySH,Gly; since CySH is common to both dipeptides it must, in the tripeptide, be in the middle. In a more complicated case, such as those presented as problems at the end of the chapter, the evidence may disclose that a particular amino acid unit fits into the chain at two or more positions.

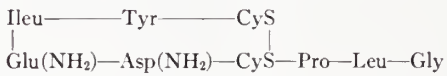
18.26 **Oxytocin, a Peptide Hormone.** — The pituitary gland of the brain produces the hormone oxytocin, which effects contraction of the pregnant uterus and hastens childbirth. The Nobel Prize for 1955 was awarded to Vincent du Vigneaud of Cornell Medical College for the isolation, elucidation of structure, and synthesis of oxytocin. The substance is not of high molecular weight and is a peptide, rather than a protein. On complete hydrolysis it yields eight different amino acids, one of which is the disulfide cystine, CyS—SCy. This unit conceivably could bind together two peptide chains, A and B, but,

Cleavage of a cystine bridging unit



when the disulfide link is cleaved by oxidation with performic acid to produce two sulfonic acid groups, only one reaction product is produced, not two, and its molecular weight is in the same range as that of oxytocin. Therefore chains A and B are linked together at a second point, and the hormone is a cyclic peptide. The amino acid sequence was established largely by partial hydrolysis and identification of the amino acid components of a number of di-, tri-, tetra-, and heptapeptides. The evidence eventually pointed to the structure formulated. The same conclusion was reached independently by Hans Tuppy in

Structure of the peptide



Vienna and was later confirmed by syntheses of biologically active material achieved by du Vigneaud and by Roger A. Boissonnas at Geneva, Switzerland.

18.27 **Insulin.** — Insulin is a hormone secreted by the pancreas, a gland in the abdomen, and is required for normal metabolism of carbohydrates. Deficiency of the hormone leads to diabetes, a disease in which carbohydrates in the diet are not oxidized in the normal way to carbon dioxide and water with energy release, but are largely excreted in the urine. A procedure for preparation from the pancreas of sheep or oxen of an active extract suitable for treatment of diabetic patients to promote utilization of sugar was developed by Banting and Macleod at the University of Toronto in 1912. Crystalline insulin was later isolated by isoelectric precipitation and found to have the relatively low molecular weight of 12,000. The hormone has a high content of

Deficiency causes diabetes

cystine and is built up of four polypeptide chains bound together in a three-dimensional sheaf by four disulfide linkages of cystine. On oxidation with performic acid the disulfide linkages are severed and the molecule cleaved to two molecules of peptide A and two of peptide B. By end-group analysis and partial hydrolysis, Sanger worked out the complete amino acid sequence of both peptides.

Structure

Adrenocorticotropic Hormone (ACTH). — This hormone is produced in the pituitary gland of the brain and carried in the blood stream to the adrenal gland near the kidney, where it stimulates production of the steroid hormone cortisone (17.6). The hormone is a mixture of related proteins of molecular weight about 20,000. One of the physiologically active components, β-corticotropin, was investigated extensively by two American research groups, both of which in 1955 reached the conclusion that the amino acid sequence is that

18.28

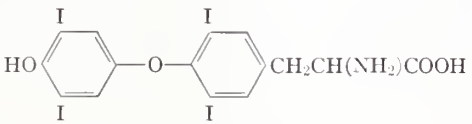
Sequence of the 39 amino acid units determined

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Try-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asp-Gly-Ala-Glu-Asp-Glu-Leu-Ala-Glu(NH_2)-Ala-Phe-Pro-Leu-Glu-Phe

formulated. The amino-terminal group (to the left) is serine, and the carboxy-terminal group (to the right) is phenylalanine.

Thyroglobin. — This hormone of the thyroid gland of the neck is a protein whose function is to maintain metabolic activity of cells. The disease resulting from thyroglobin deficiency is characterized by dry skin, swollen tissue, and lowered rate of metabolism. Dramatic cures are obtained by administration of the hormone. This protein is characterized by the presence of an unusual amino acid containing iodine, thyroxine.

18.29

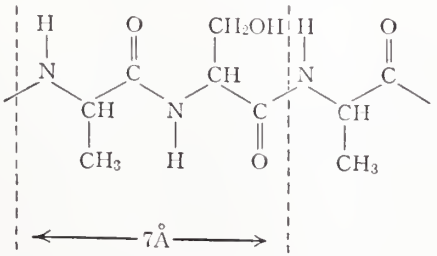


Thyroxine

Iodine-containing amino acid

Fibroin. — This fibrous (insoluble) protein of silk is made up largely of four neutral amino acids, two with hydroxyl groups and two without. X-ray analysis reveals an identity period of 7Å along the

18.30



Fibroin (?)

Silk protein

fiber axis corresponding to that expected for a pair of neutral units such as that formulated on the preceeding page.

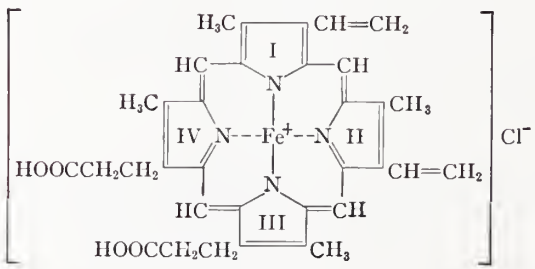
18.31 **Hemoglobin.** — The solid content of the red blood corpuscles of mammals contains on the average 32% of the conjugated protein hemoglobin. This protein is easily isolated in crystalline form from the solution prepared as described previously by separation and hemolysis of red blood cells. The solution is shaken with oxygen to produce the oxygenated form, oxyhemoglobin, treated with alcohol, and kept at −20° until deep red crystals separate. Values for the percentage composition vary slightly for different animal species, but a typical empirical formula is $(C_{738}H_{1166}O_{208}N_{203}S_2Fe)_n$. Iron is the element present in smallest equivalent amount, and since at least one atom of the element must be present the iron content fixes the minimal molecular weight. Values calculated on this basis are in the range 16,500–17,000. Ultracentrifuge determinations give an average molecular weight of 65,500, or four times the minimal value; hence n in the formula has a value of four.

Contains iron

18.32 On careful treatment with hydrochloric acid the conjugated protein is cleaved into the fragments hemin (4%) and globin (96%). Hemin has the formula $C_{34}H_{32}O_4N_4FeCl$; the iron corresponds to the total present in hemoglobin and the chlorine atom is derived from the hydrochloric acid used for cleavage. Hemin is the chloride of the parent substance heme, $C_{34}H_{32}O_4N_4FeOH$, which is the oxidized form (ferric) of the true prosthetic group of the conjugate. Although far simpler than the original protein, the hemin molecule presents a structure that is both unusual and elaborate, as can be seen from the formula, and the problem of elucidating the structure was solved

Hemin + globin

Structure of the prosthetic group



Hemin

eventually only as the result of exhaustive researches extending over a period of forty years, conducted by a succession of German chemists and culminating in the synthesis of hemin by Hans Fischer in 1930 (Nobel Prize, 1930). Four pyrrole rings are connected by the bridging group —CH=. These rings are substituted with methyl, vinyl, and propionic groups. The iron atom is bound to all four nitrogen atoms by either primary valence bonds or by partial valences. The iron-free

compound is of a type described as a porphyrin. Chlorophyll, the green pigment of plants, is a magnesium-containing porphyrin and has been correlated with hemin by conversion to a common degradation product.

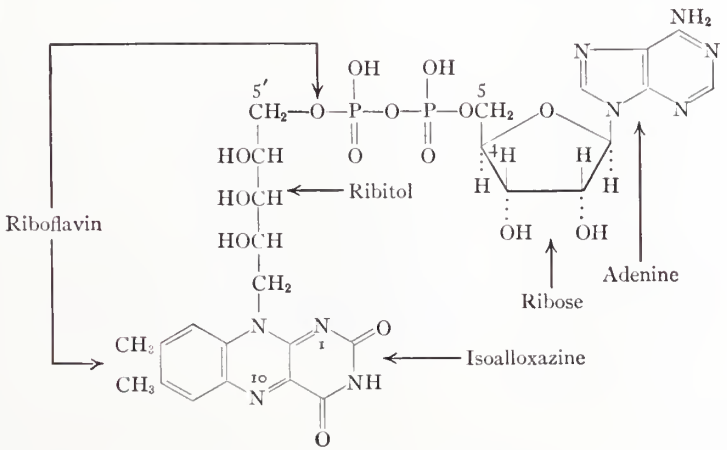
Enzymes. — In 1897 the German chemist Eduard Buchner established that a cell-free aqueous solution prepared by grinding yeast with sand and filtering the solution through a fine-pore filter contains substances capable of promoting fermentation of sugars to alcohol and carbon dioxide (16.21; Nobel Prize, 1907). Biochemical studies by many subsequent investigators revealed the many steps in the complicated but efficient process and showed that each is controlled by a specific catalyst, an enzyme. In 1926 James B. Sumner of Cornell Medical College succeeded for the first time in isolating an enzyme in pure, crystalline form and characterized it as a protein (Nobel Prize, 1946). This enzyme, urease, acts on urea and promotes its decomposition to carbon dioxide and ammonia. Many other enzymes have since been isolated, and they are all proteins. Some promote hydrolysis (and resynthesis) of esters and are called esterases or hydrolases, and others catalyze hydrolysis of proteins and are called proteolytic enzymes; enzymes of these two types are completely proteinoid in make-up and are called simple proteins.

18.33

Hydrolases (-ase designates an enzyme)

Enzymes that control processes of oxidation and of reduction are conjugated proteins containing a prosthetic group, comparable to heme of hemoglobin, in which the capacity for oxidation-reduction resides. In one, a yellow enzyme, the prosthetic group attached to protein is flavin adenine dinucleotide FAD, in the formula of which the component parts are indicated. The term dinucleotide means that the substance is a diphosphate (pyrophosphate) ester. The

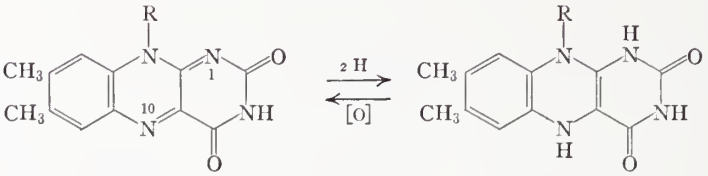
18.34



Flavin adenine dinucleotide (FAD)

Prosthetic group of an oxidase-reductase

isoalloxazine group is responsible for the yellow color and functions as hydrogen acceptor; hydrogen adds 1,4 to the unsaturated system extending between N_1 and N_{10} to form a colorless dihydride, $FADH_2$,



FAD (yellow) $FADH_2$ (colorless)

from which the pigment is regenerated by oxidation. Isoalloxazine itself is insoluble in water, but the hydroxyl groups of the two sugar units, fortified by those of the pyrophosphate unit, render the molecule soluble. The acidic pyrophosphate group is balanced by the basic group of adenine. A prosthetic group is also called a coenzyme and is effective only in combination with a specific protein in the form of the complete enzyme. By careful treatment with an acid or with alcohol, an enzyme can often be split into the specific protein in its native form and the coenzyme, or prosthetic group. Neither component alone is effective as a biological catalyst, but activity is restored when solutions of the components are mixed.

SUMMARY

Fibrous proteins (water-insoluble): fibroin (silk), collagen (boiling water ⟶ gelatin), keratin (skin, wool), elastin. Globular proteins (water-soluble at proper pH): egg albumin, casein, hemoglobin (conjugated, contains the prosthetic group heme). Plasma proteins: albumins, globulins, lipoproteins, fibrinogen, prothrombin. Serum from clotted blood lacks fibrinogen, which in clotting is converted to fibrin.

Polypeptide nature of proteins; hydrolysis to amino acids; reformation from amino acids of plant proteins.

Amino Acids

Neutral: glycine, and its homologs alanine, valine, leucine, isoleucine; phenylalanine and tyrosine (p-OH); proline (5-ring); tryptophan (β-indoloalanine); cysteine (β-SH-alanine), cystine (disulfide), and methionine (S-methylhomocysteine); serine (β-OH-alanine) and threonine (β-CH_3-serine). Acidic: aspartic (α-NH_2-succinic) and glutamic (α-NH_2-glutaric); also their monoamides asparagine and glutamine. Basic: lysine (α,ϵ-di-NH_2-caproic) and arginine (α-NH_2-δ-guanidyl-valeric).

Isoelectric point (pH of charge balance, dipolar ion form predominates): alanine type, 6.0; aspartic acid type, about 2.0; lysine, 9.7; arginine, 10.8.

Configuration: all belong to L-series (NH_2 to left), related to L(+)-lactic acid.

Isolation. Hydrolysis with acids or with enzymes. Ester-distillation of neutral components. Precipitation with $HgSO_4$ (tryptophan), with phosphotungstic acid (basic amino acids).

Synthesis. Enzymatic resolution through N-acetyl deriv. Amination of α-halo acids. Strecker synthesis ($RCHO \longrightarrow RCH(NH_2)CN \longrightarrow RCH(NH_2)CO_2H$).

Isolation. Isoelectric salting out or precipitation with ethanol. Slow addition of $(NH_4)_2SO_4$ by dialysis to promote crystallization.

Amino acid analysis. Paper chromatography (color reaction with ninhydrin). Microbiological assay (specific acids required for normal growth). Isotope dilution method.

Amino acid sequence. End-group analysis by reaction with 2,4-dinitrofluorobenzene, hydrolysis, and identification of the labeled amino acid.

Glutathione: Glu—CySH—Gly. Deduction of structure from end-group analysis and by identification of the components of dipeptides produced on partial hydrolysis.

Oxytocin, a peptide hormone. Cyclic structure, with the disulfide link of CyS—SCy closing the ring between two parts of polypeptide chain.

Insulin: protein hormone of pancreas, promotes normal metabolism of carbohydrates. Hormone isolated from animal pancreas used for treatment of diabetes. Mol. wt. only 12,000. Four polypeptide chains bound into a sheaf by disulfide links of cystine.

Adrenocorticotropic hormone (ACTH). A protein produced in the pituitary gland of the brain and carried to the adrenal gland to stimulate production of cortisone. Amino acid sequence of the 39 component acids determined.

Thyroglobin. Characteristic acid is thyroxine (4 iodine atoms).

Fibroin of silk composed chiefly of neutral amino acids.

Hemoglobin. Easily crystallized in oxygenated form: oxyhemoglobin (HbO_2). Iron analysis indicates minimal molecular weight of 16,500; actual molecular weight $4 \times 16{,}500 = 66{,}000$. Split by HCl to hemin ($C_{34}H_{32}O_4N_4FeCl$) and globin (globular protein, 96% of whole). Actual prosthetic group is heme. Hemin made of four pyrrole rings joined by methine links (—CH=).

Enzymes. Isolated in crystalline form (Sumner). Are all proteins. Hydrolases (split esters) and proteolytic enzymes are all-protein. Oxidases-reductases contain a prosthetic (attached) group containing an oxido-reduction function. Prosthetic group, or coenzyme, of yellow enzyme is flavin adenine dinucleotide, which has a reducible, pigmented group solubilized by ribose units and a pyrodiphosphate group whose acidity is balanced by a basic group (adenine).

PROBLEMS

1. Write the formula of a hypothetical polypeptide having an excess of acidic over basic groups and of highly hydrophilic character.
2. Formulate a hypothetical polypeptide having a disulfide bridge between two chains and meeting the following specifications: nearly neutral; highly hydrophobic (lipophilic).
3. Explain why the dinitrophenyl derivative of alanine is easily differentiated from alanine by paper chromatography.
4. A pentapeptide on treatment with 2,4-dinitrofluorobenzene, followed by hydrolysis, gave a yellow derivative identified as

   $2,4\text{-}(NO_2)C_6H_3NHCH(CH_2CH_2SCH_3)CO_2H.$

   Partial hydrolysis of the pentapeptide gave a mixture from which four dipeptides were isolated. Each of the dipeptides was hydrolyzed and the component acids identified, but the amino acid sequence in each dipeptide was not determined. Deduce the structure of the pentapeptide. The dipeptides:

Asp,Met	Tyr,Ser
Ser,Phe	Asp,Phe

5. End-group analysis of a heptapeptide gave a 2,4-dinitrophenyl derivative identified by paper chromatography as that of glycine. The heptapeptide was partially hydrolyzed and a number of di- and tripeptides were isolated from the mixture. Each pure peptide was then hydrolyzed completely and the component acids identified, but the peptides were not submitted to end-group analysis. Deduce the amino acid sequence in the heptapeptide. The peptides:

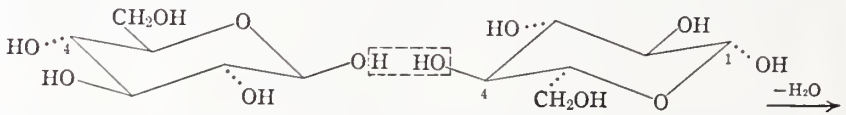
Ala,Gly	Met,Ala,Glu
CySH,Glu	Leu,Ala
Ala,CySH	Leu,Ala,Met

CHAPTER 19

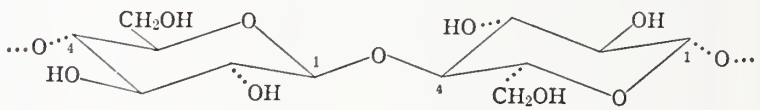
POLYMERS

19.1 *Cellulose*

The term polymer is applied to substances composed of at least 100 repeating units, and often many times that number. Cellulose is a natural polymer formed from the monomer glucose by elimination of water between successive units of the cyclic β-form. A reaction involving elimination of water between monomer units is described



β-D-Glucopyranose



Cellulose

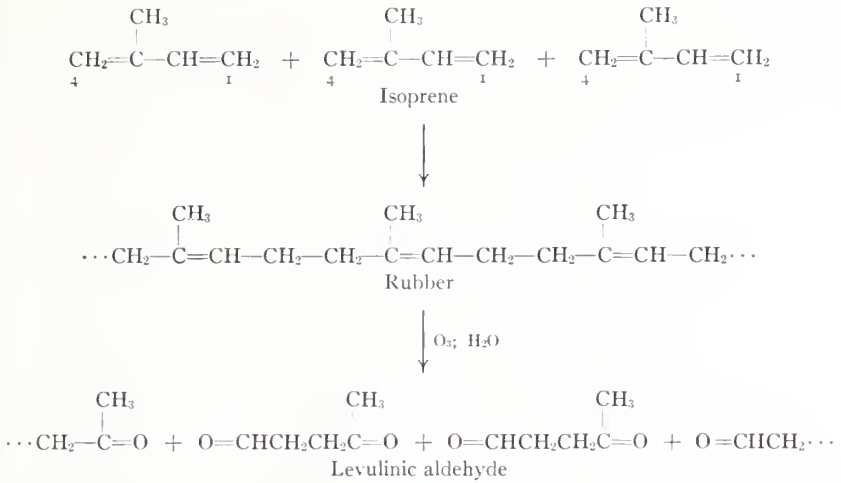
Proteins

as a condensation polymerization. Proteins are products of condensation polymerization of units of the same general type but having varying side chains.

19.2

Natural Rubber. — In contrast to cellulose and proteins, rubber is an addition polymer formed by multiple condensation of an unsaturated monomer and has the same composition as the monomer. The monomer is isoprene, C_5H_8, and rubber has the formula $(C_5H_8)_n$. Like other natural isoprenoids (17.8–17.10), rubber can be regarded as derived from the diene isoprene by multiple 1,4-addition. That the isoprene units are joined head-to-tail, or 1,4, was established by oxidative degradation to levulinic aldehyde. The fission of the double bond to produce a keto group on one side and an aldehyde group on the other can be done by reaction with ozone, or ozonization.

Structure by ozonization



Monomer

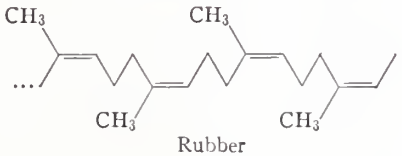
Polymer

which accomplishes in one step the same result as hydroxylation and *vic*-glycol cleavage (4.15).

Rubber contains one double bond per C_5 unit and, as is shown by the result of ozonization, this is at the 2,3-position in the isoprene unit. Unstretched rubber shows no regular X-ray diffraction pattern and is, therefore, amorphous, but stretched rubber has an oriented, ordered structure characteristic of crystallinity, and analysis of the X-ray pattern leads to the conclusion that rubber has the all-*cis* configuration. The unsaturated character of the rubber hydrocarbon

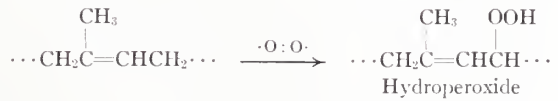
19.3

X-ray analysis of stretched rubber



All-cis

is responsible for its deterioration on aging. Aging is due to air oxidation, and probably the first step is allylic oxidation to a hydroperoxide, as in the setting of a drying oil (17.20). Succeeding steps appear to clip the chain at or near the points attacked with resulting



Aging = oxidation

lowering of the average molecular weight and decrease in strength and elasticity. Phenols and arylamines that are sensitive to oxidation are incorporated into rubber stock because they function as antioxidants and materially prolong the life of rubber articles.

The chief source of the world's supply of rubber is the tree *Hevea brasiliensis*, cultivated in plantations in the Malay Peninsula, the

19.4

Latex

Dutch East Indies, and Ceylon. When an incision is made through the outer bark of the rubber tree, a milky fluid called latex oozes out. This is a colloidal dispersion of rubber particles in water and contains about 35% of rubber and a protective protein that stabilizes the emulsion. Some latex is used as such for special items. Balloons, gloves, shoes, bathing caps are made by dipping a mold into compounded latex, drying the adhering film on the form, and then curing it. Sponge rubber is made by whipping air into compounded latex. The bulk of the plantation latex is coagulated by addition of acetic acid and the cheeselike precipitate is rolled or milled into sheets of raw rubber. This rubber is tacky, soft, and of low-grade strength and elasticity. All these properties are improved markedly by the process of vulcanization (Charles Goodyear, 1838), which consists in heating rubber with 5–8% of sulfur. The initial attack by sulfur probably is not at a double bond but at an allylic position, as in air oxidation. The end result appears to be establishment of sulfur cross links between parallel hydrocarbon chains.

Raw rubber

Vulcanization

19.5 Synthetic Rubbers (Elastomers). — Early workers, finding that rubber on destructive distillation is depolymerized to isoprene, sought to reverse the process and were, indeed, able to obtain from the liquid monomer products that superficially resembled rubber. No practical application ensued until World War I, when the blockade cutting off Germany from supplies of natural rubber stimulated research on the problem and led to small scale production of the first synthetic rubber, a polymer of 2,3-dimethylbutadiene. This rubber had poor physical properties and attained no importance. A much better product, introduced in Germany in 1927, was made by polymerization of butadiene with sodium as catalyst; it was called Buna rubber (butadiene-Natrium, German for sodium).

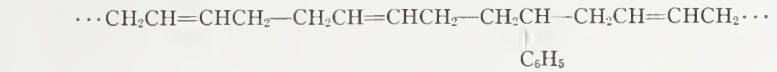
Buna rubber from butadiene

19.6 A major contribution to further development of synthetic rubbers was the introduction of the technique of emulsion polymerization, suggested by the fact that natural rubber occurs as an emulsion. The monomer is dispersed in 2–4 parts of water with the aid of an emulsifying agent (fatty acid soap) and a protective colloid (gelatin), and polymerization is maintained at a suitable rate by controlled addition of a polymerization catalyst. Emulsion polymerization permits accurate control of the degree of polymerization, is rapid, and lends itself well to incorporation of modifying agents. The process has the particular advantage of permitting copolymerization, that is, use of more than one building unit. The most important rubber substitute is a copolymer of butadiene and styrene ($C_6H_5CH{=}CH_2$), known as GRS rubber (Government Rubber Styrene). In the commercial product used in the manufacture of tires the ratio of butadiene to

Emulsion polymerization

GRS rubber

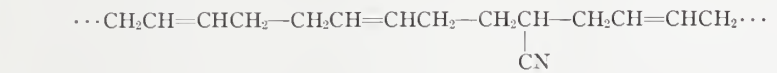
styrene is about 3:1. Another important rubber, known as Perbunan



GRS rubber

Copolymer of butadiene and styrene

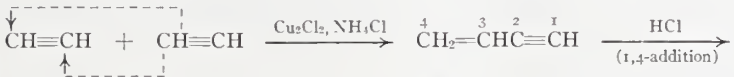
or Hycar rubber, is a copolymer of butadiene with about 25% of acrylonitrile, $CH_2{=}CHCN$.



Hycar rubber

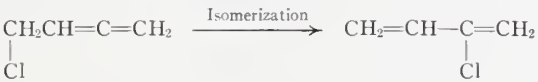
Copolymer of butadiene and acrylonitrile

Neoprene Rubber. — Discovery of this first American synthetic rubber (1932) was the outcome of fundamental studies on the chemistry of acetylene by Father Nieuwland, professor of chemistry at the University of Notre Dame. du Pont chemists headed by Wallace H. Carothers extended this work and perfected a process for dimerization of acetylene to vinylacetylene, which adds hydrogen chloride to form chloroprene, of structure analogous to that of isoprene. Chloroprene



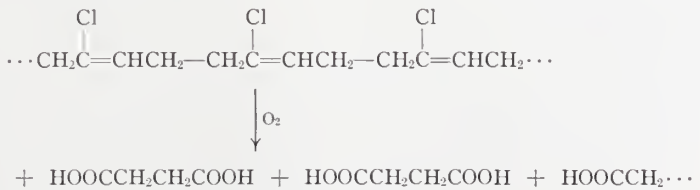
Vinylacetylene

Monomer: chloroprene

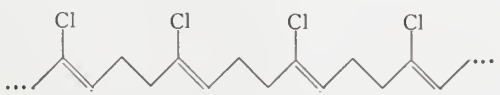


Chloroprene

polymerizes very rapidly and gives a polymer which can be vulcanized to the finished product neoprene. The chains are formed by 1,4-addition, for oxidation gives succinic acid as the main product.



X-ray analysis has established the *trans*-configuration. Neoprene is too expensive for use in tires but has many special uses because of its



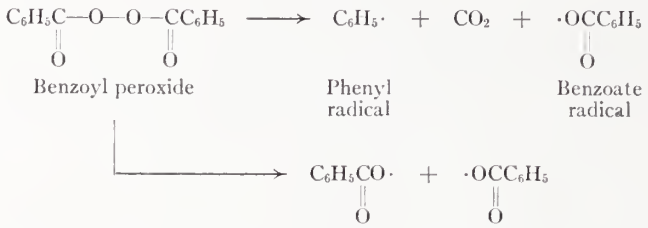
Neoprene

All-trans

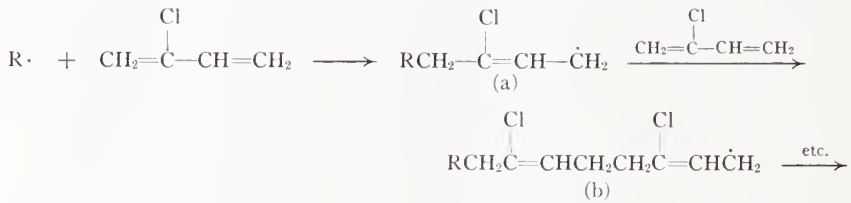
superior resistance to organic solvents, chemicals, and air oxidation.

Mechanism of Polymerization. — That the polymerization of a

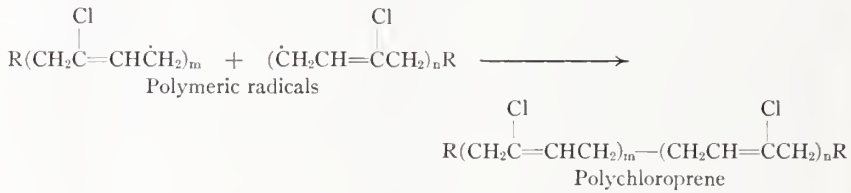
diene is a free-radical reaction is evident from the fact that it is catalyzed by benzoyl peroxide, a substance which readily yields radicals by decomposing with liberation of carbon dioxide, or simply by homolysis. A radical, represented as R·, initiates a chain reaction by



combining with monomer to form another radical (a). This radical adds another monomer to form (b), and the process continues. The



polymeric radical grows very rapidly, and eventually the chain is terminated by combination of two polymeric radicals to form a stable polymer molecule.



19.9 **Cellulose Derivatives in Technology.** — The silkworm, which exists on a diet consisting largely of cellulose from mulberry leaves, produces a viscous solution of the nitrogen-containing protein fibroin. The protein is secreted from two glands, each of which communicates by a duct with a tiny orifice (spinneret) located near the lip. After a drop is attached to an object, the silkworm draws a thread by moving its head and forefeet. The two filaments are cemented by a sticky protein, a silk glue. Cellulose, with three hydroxyl groups per C_6-unit, is as insoluble in organic solvents as it is in water, and processes for making silk substitutes from wood pulp cellulose involve conversion to a less hydroxylic derivative that can be dissolved in an organic solvent to give a viscous solution capable of being extruded under pressure through a die containing capillary orifices to produce a number of filaments that can be twisted together to form a thread.

Pattern of the silkworm

The nitrocellulose process, the first known for making artificial silk, was discovered by Count Hilaire de Chardonnet in 1855. Cellulose is nitrated in the presence of sulfuric acid under conditions such as to

Nitrocellulose process

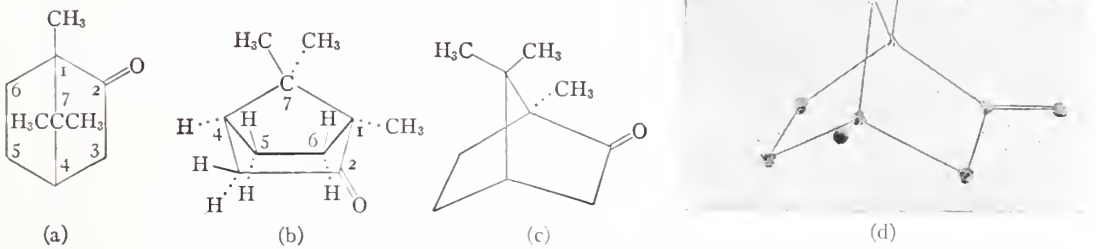
$$[C_6H_7O_2(OH)_3]_n \xrightarrow{HNO_3,\ H_2SO_4} \underset{\text{Cellulose dinitrate}}{[C_6H_7O_2(OH)(ONO_2)_2]_n} + H_2O$$

give material approximating the dinitrate and known as pyroxylin; exhaustive nitration gives the trinitrate ester, guncotton. Pyroxylin dissolves in a mixture of alcohol and ether to form a viscous solution, collodion, which is forced through the orifices of a die into an atmosphere of dry air to evaporate the solvent. The nitrate groups are then removed by passage through a bath of sodium hydrosulfide solution. The denitrated thread of regenerated but somewhat altered cellulose resembles silk in appearance but is of rather poor quality.

A second use for pyroxylin is in production of the cellulose nitrate plastic celluloid (cellulose + oid), which is cellulose dinitrate plasticized with about 20% of camphor. Camphor, $C_{10}H_{16}O$, is a terpene ketone, and the structure (a) can be separated into two units of isoprene by severance of bonds 1,7, 3,4, and 5,6. Formula (b) shows

19.10

Celluloid



(a) (b) (c) (d)

that the cyclohexanone ring is locked in the boat conformation by the C_7-*gem*-dimethyl bridge linked to bow (C_1) and stern (C_4). Formula (c) is a projection of (b) after this has been turned to an angle of about 45° to bring C_4 to the front and C_1 to the rear as in the model (d). Natural camphor, m.p. 179°, α_D +44°, comes from a tree indigenous to the island of Formosa, and *dl*-material is synthesized from the terpene hydrocarbons α- and β-pinene ($C_{10}H_{16}$), the chief constituents of turpentine from pine resin. The two solids pyroxylin and camphor are gelatinized with alcohol, which promotes plastic flow during molding and is removed in a curing operation.

Modified pyroxylin has an important use in the production of

19.11

Nitrocellulose lacquers

quick-drying lacquer paints for automobiles, which dry by evaporation of the solvent. The modification required is obtained by partial depolymerization, effected by heating pyroxylin under pressure with very dilute acid, to increase the solubility in organic solvents and reduce the viscosity of the solutions. Butyl acetate is the preferred solvent.

19.12 Acetylation of the hydroxyl groups of cellulose also increases solubility in organic solvents and thermoplasticity, and material corresponding approximately to the diacetate is employed as a fiber (acetate rayon) and as a molding plastic. Acetone is used as a solvent for spinning, and the extruded filaments are dried in warm air. In the viscose process for making rayon, wood pulp is compounded with sodium hydroxide to give a salt, alkali cellulose, which reacts with

Cellulose acetate

Viscose rayon

$$[C_6H_{10}O_5]_n \xrightarrow{NaOH} \underset{\text{Alkali cellulose}}{[(C_6H_{10}O_5)_2\cdot NaOH]_n} \xrightarrow{CS_2} \underset{\text{Cellulose xanthate}}{\left[(C_6H_9O_4)_2\cdot OH\cdot OC\begin{matrix}\diagup\!\!=S\\ \diagdown SNa\end{matrix}\right]_n} + n\,H_2O$$

carbon disulfide to yield a xanthate. This derivative forms a viscous colloidal solution in dilute aqueous alkali, which is ripened, filtered, and extruded through a die into a bath of dilute sulfuric acid. The acid regenerates cellulose, and the fibers are then bleached and dried. Cellophane is made by extruding the viscose sirup through a slit into an acid bath to form a sheet of regenerated cellulose, which is rendered soft and pliable by passage through a solution of glycerol.

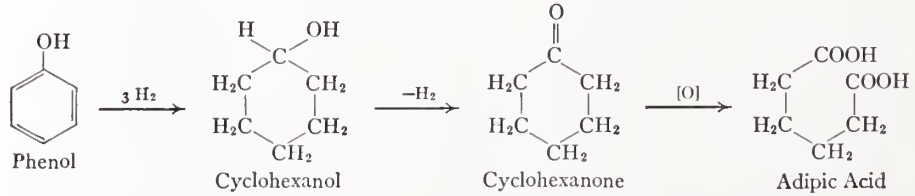
19.13 **Nylon,** a superior fiber developed by Carothers and introduced by du Pont in 1940, is a polyamide made by condensation polymerization of a mixture of adipic acid and hexamethylenediamine, both of which are made from phenol. This starting material is converted through

$$HO{-}\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}{-}OH + H_2N(CH_2)_6NH_2 \xrightarrow{-H_2O}$$

$$\cdots\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}NH(CH_2)_6NH\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}NH(CH_2)_6NH\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}NH(CH_2)_6NH\cdots$$

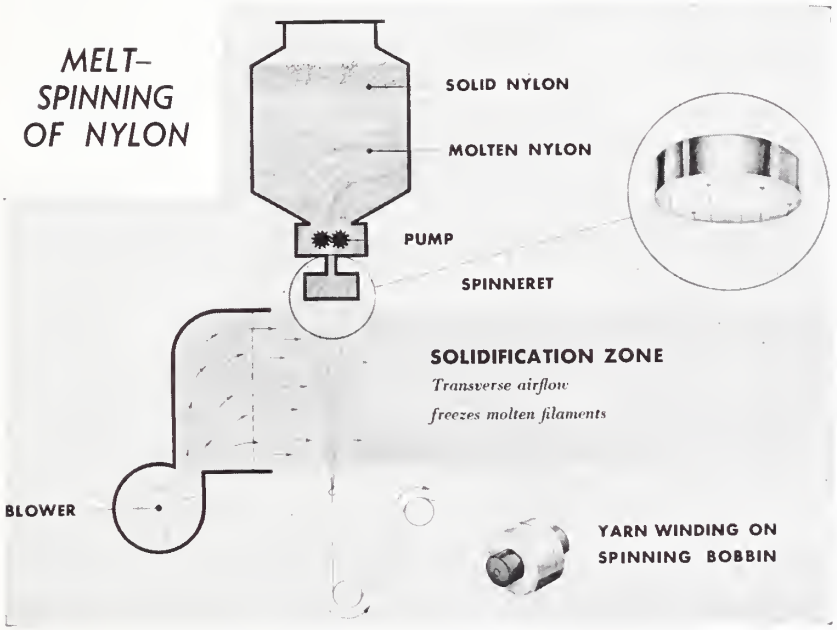
cyclohexanol into cyclohexanone and then on oxidation into adipic acid, a part of which is converted into the desired diamine. Con-

Source of components



$$\xrightarrow{NH_3} \underset{\text{Adipamide}}{H_2N{-}\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}{-}NH_2} \xrightarrow{-H_2O} \underset{\text{Adiponitrile}}{N{\equiv}C(CH_2)_4C{\equiv}N} \xrightarrow{4\,H_2} \underset{\text{Hexamethylenediamine}}{H_2NCH_2(CH_2)_4CH_2NH_2}$$

densation of the components is effected by heating in an autoclave. The polymer melts at 263° and filaments are made by extruding the molten material through fine orifices and freezing them in a current of air. Nylon is structurally related to fibroin, the protein of silk



Melt-spinning of nylon. Courtesy of the du Pont Company.

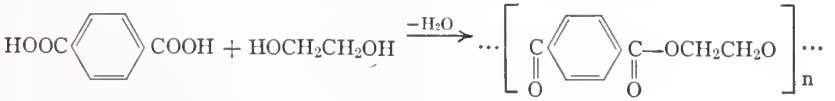
(18.30), since both are essentially neutral polyamides. The synthetic polyamide has a higher tensile strength than silk, it is tough and of good chemical stability, and it excels in abrasion resistance.



Nylon

A polyamide fiber

Dacron is a polyester fiber made by esterification of terephthalic acid, a diacid, with ethylene glycol, a diol. The fiber has high tensile



Terephthalic acid

Condensation polymer

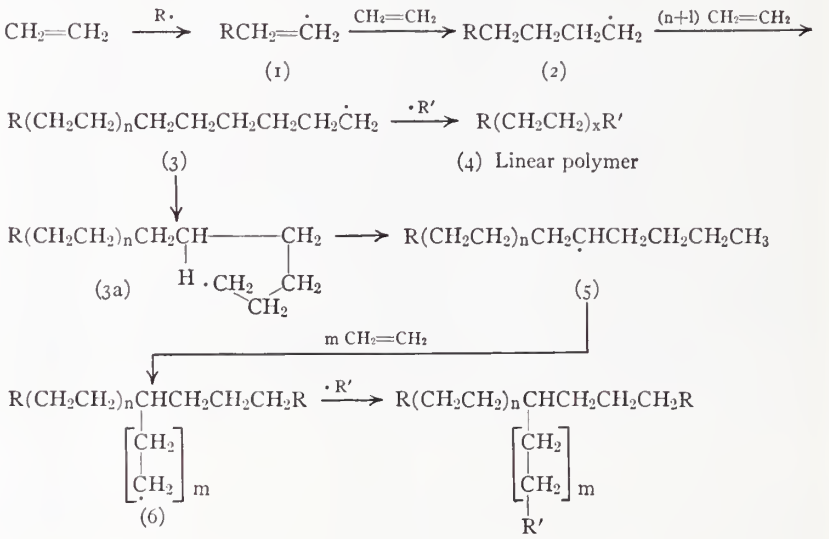
strength and resiliency and is surprisingly stable to fairly severe hydrolytic treatment; ordinary esters are not so resistant to hydrolysis as amides. Garments made of it are markedly crease-resistant.

Polyethylene. — Articles made of polyethylene plastic have be-

come commonplace: bags for fruits and vegetables, plastic bottles, pails, trash barrels, etc. The original process involved polymerization of ethylene at high temperatures and pressures with a peroxide catalyst to give a solid polymer melting at about 110° and capable of being molded. Polyethylene plastic is tough and flexible, and it possesses excellent electrical insulation characteristics and high water resistance.

19.16 Free-radical initiated polymerization involves a growing chain with an odd electron on the terminal carbon (1–3). Some of the final chains are linear (4), but others become branched. If the growing

Mechanism of polymerization



chain (3) bends back on itself (3a) as if to form a five- or six-membered ring, a hydrogen atom can be picked off at the point concerned to give a radical (5) with the odd electron at what becomes a branching point to give (6) and (7). The density of the plastic is an index of its structure: the higher the density the greater is the degree of linearity.

19.17 In 1954 Karl Ziegler of the Max Planck Institute for Coal Research in Germany developed a new type of catalyst which makes possible the polymerization of ethylene at atmospheric pressure. Advantages of the low-pressure process are evident from the fact that eight U.S. companies promptly obtained Ziegler licenses from the Institute at a cost of $8–9 million and readied 30-million-pound plants to go into continuous-process production (in the language of the industry, "to go on stream"). Polymerization is done at atmospheric pressure and at only slightly elevated temperature, and high purity ethylene is not essential. The low-pressure process gives

Low-pressure polyethylene

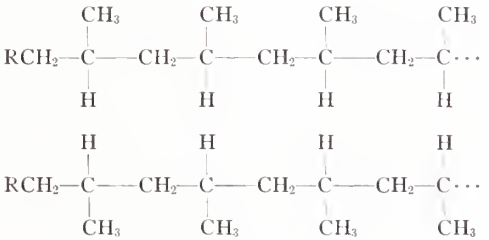
polyethylene of greater linearity than the earlier material, as reflected in an increase in density from 0.92 to 0.96, and it is characterized by a higher softening temperature, greater rigidity, and better tensile strength.

19.18

Ziegler catalyst

A typical Ziegler catalyst is prepared by reaction of a trialkylaluminum, AlR_3, with titanium tetrachloride in benzene solution; the catalyst separates as a finely divided precipitate. It is believed that the growing end of the polymer radical, that is, the odd-electron carbon atom formulated above in (1) and (2), remains fixed at an active site of the catalyst surface and that added monomer units therefore are always fed onto the chain in the same steric sense. This accounts for the linearity of the polymer and also for a remarkable polymer obtained from propylene. In the chain $RCH_2CH(CH_3)—CH_2CH(CH_3)—$ every other carbon atom is asymmetric, and in polypropylene prepared with ordinary catalysts the distribution of *d*- and *l*-centers is perfectly random. Ziegler catalyst, however, produces polymer in which the asymmetric centers in a given chain are all *d* or all *l*. No optical activity develops, since

Stereospecific polymerization

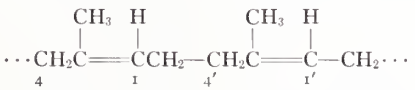


Isotactic polypropylene

the total number of *d*- and *l*-centers are equal, but the polymer has a high degree of crystallinity. A polymer of this remarkable type is called isotactic (G. Natta, Italy).

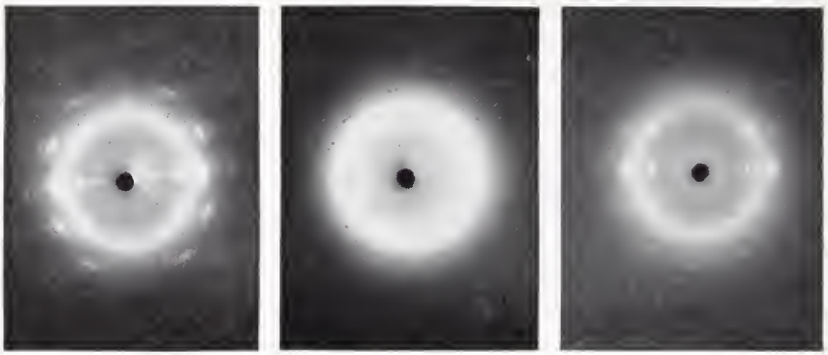
19.19

The most striking development was announced independently in 1955 by two American rubber companies. Natural rubber is all *cis*-1,4-polyisoprene; that is, the double bonds all have the *cis*-configuration and each isoprene unit is linked at the 1-position to the 4(4′)-position of a second unit. Emulsion polymerization of isoprene



gives a product (emulsion polyisoprene) of inferior quality which is part *cis* and part *trans* and in which the isoprene units are linked at random in the 1,4-, 1,2-, and 3,4-positions. The fiber diagram of this material, Fig. 1b, does not show the spots characteristic of crystallinity

as does natural rubber, Fig. 1a. Polymerization of isoprene with a Ziegler solid-surface type catalyst gives synthetic rubber that is



(a) (b) (c)

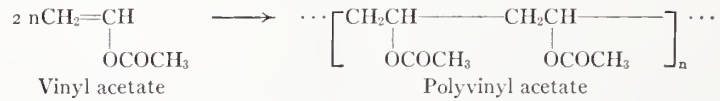
FIG. 1.— X-ray Fiber Diagroms of Stretched Rubbers: (a) Natural Hevea Rubber, (b) Emulsion Polyisoprene, (c) Synthetic *cis*-1,4-Polyisoprene. (Courtesy of the Goodyeor Tire and Rubber Company.)

"Synthetic natural rubber"

nearly all *cis*-1,4-polyisoprene. The X-ray fiber diagram, Fig. 1c, shows most of the spots characteristic of natural Hevea rubber, and the infrared spectrum (Fig. 2) is almost identical with that of natural rubber. The synthetic rubber fully matches in quality the polymer produced by the rubber tree.

19.20 **Vinyl Polymers.** — Vinyl acetate, prepared by addition of acetic acid to acetylene (3.24), can be polymerized by the emulsion technique under the catalytic influence of benzoyl peroxide to produce polymers ranging in an average molecular weight from 4300 to 100,000. Plastics

Head to tail



and molding resins suitable for a variety of purposes are available by control of the degree of polymerization, and also by subsequent hydrolysis to polyvinyl alcohol, or by partial hydrolysis to products containing both acetyl and hydroxyl groups.

19.21 Vinyl chloride similarly affords polyvinyl chloride; as in the case of the acetate, the monomer units are linked head to tail. Polyvinyl

Polyvinyl chloride



chloride, a solid, is plasticized with dioctyl phthalate, a liquid, to produce a rubberlike, translucent material (Tygon) used in the laboratory like rubber tubing. Dioctyl phthalate is made by esterification of phthalic anhydride with 2-ethylhexanol-1, which is manu-

Tygon

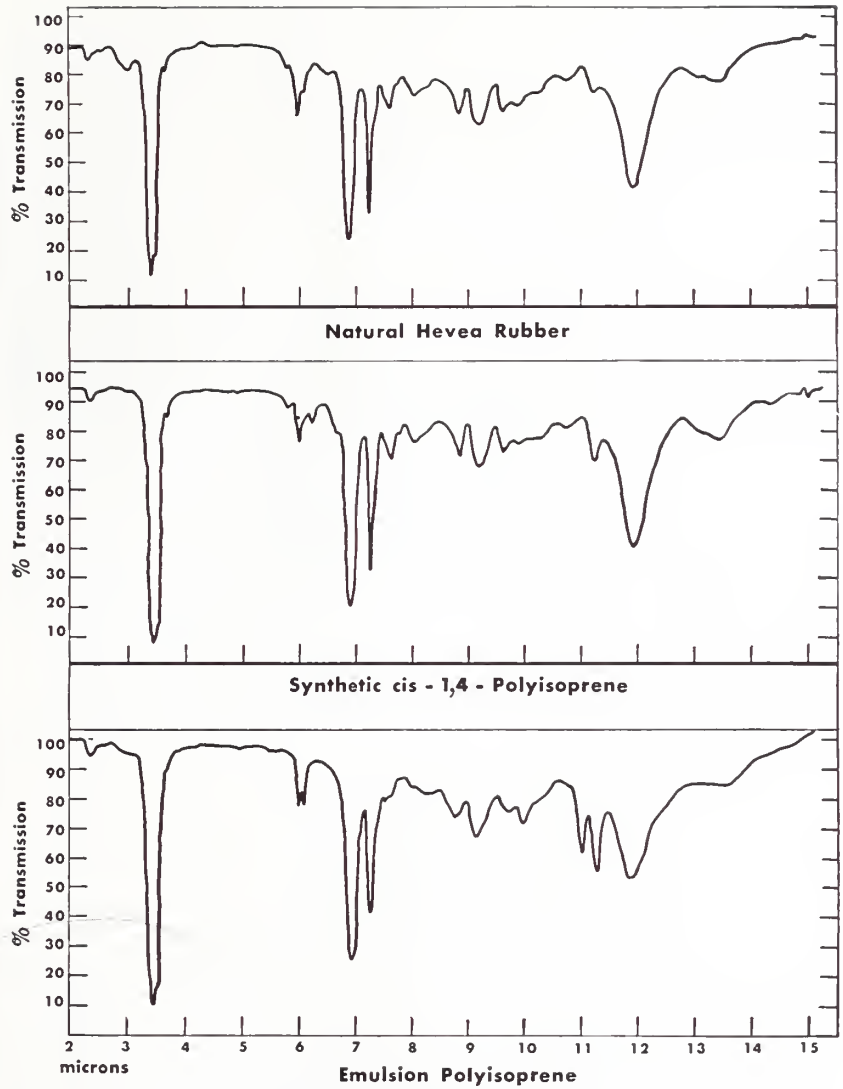


FIG. 2.— Infrared Spectra. (Courtesy of the Goodrich-Gulf Chemical Company.)

factured from *n*-butyraldehyde by aldol condensation, dehydration, and hydrogenation.

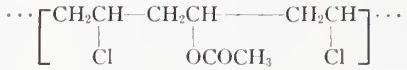
$$CH_3CH_2CH_2CHO + \underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CH_2CHO}{|}} \xrightarrow{OH^-} CH_3CH_2CH_2\underset{\displaystyle OH}{\overset{\displaystyle CH_2CH_3}{|}}CH{-}\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CHO}{|}} \xrightarrow{-H_2O}$$

$$CH_3CH_2CH_2CH{=}\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CCHO}{|}} \xrightarrow{2\,H_2} CH_3CH_2CH_2CH_2\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CHCH_2OH}{|}}$$

2-Ethylhexanol-1

19.22 Copolymers of vinyl acetate and vinyl chloride are useful both as plastics and as fibers. Vinyon is a fiber produced by emulsion polymerization of 12% of vinyl acetate with 88% of vinyl chloride. The

Copolymer fiber



Vinyon

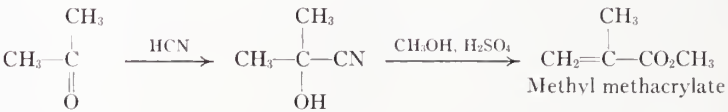
dope for spinning fibers is a solution of the fluffy copolymer (mol. wt. about 20,000) in acetone.

19.23 **Polystyrene.** — Styrene, which on copolymerization with butadiene gives a rubber, or elastomer (19.6), is polymerized alone in an emulsion of 5% sodium oleate to a polymer of high molecular weight that is thermoplastic and can be softened and molded.



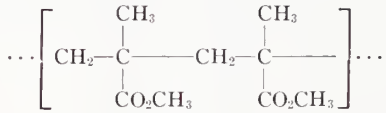
Polystyrene

19.24 **Methacrylate Plastic.** — Methyl methacrylate, another vinyl monomer, is available from acetone by way of the cyanohydrin.



Methyl methacrylate

Methyl methacrylate polymer

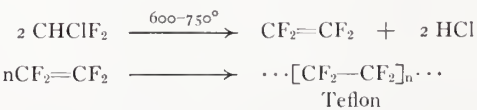


Polymer

Polymerization occurs under usual conditions; it can be conducted in solution for preparation of dopes. Methyl methacrylate polymer is molded into sheets (Plexiglas, Lucite) distinguished by colorless transparency; the material is the nearest approach known to an organic glass.

19.25 **Teflon** is the product of polymerization of another vinyl monomer. Pyrolysis of chlorodifluoromethane (1) affords tetrafluoroethylene which, on emulsion polymerization catalyzed by oxygen (2) yields Teflon, a polymer of unusual properties (du Pont). Teflon has un-

Contains no hydrogen



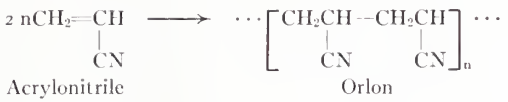
Teflon

rivaled resistance to solvents and to boiling acids, even aqua regia, and is stable to temperatures up to about 325°. A mixture with graph-

ite is cold-pressed into special service gaskets by powder metallurgy technique. Tape cut from a block with a microtome is used to insulate electrical wire.

Orlon. — Acrylonitrile, or vinyl cyanide, is available by addition of hydrogen cyanide to acetylene (3.22). This vinyl derivative had been known for many years to be capable of polymerization, but the

19.26

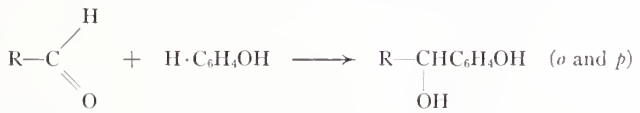


Polyacrylonitrile fiber

polymer was not considered for use as a fiber material because of lack of solubility in common solvents. It is, however, soluble in the special solvent dimethylformamide, $HCON(CH_3)_2$, and a solution in this solvent when forced under pressure through holes in an orifice gives a fiber, Orlon. Orlon fiber is of unusual stability in the dry and wet states, and of excellent resistance to sunlight and microorganisms. It can be made to resemble either silk or wool; the synthetic textiles feel warm to the hand.

Phenol-Formaldehyde Resins. — Phenols condense readily with aliphatic and aromatic aldehydes to give initial products that can be regarded as arising from an aldol-like addition of the phenol molecule, at a reactive *o*- or *p*-position, to the carbonyl group of the aldehyde.

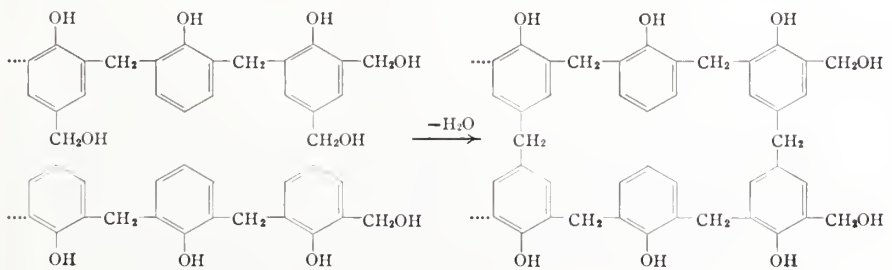
19.27



With adjustment of the proportion of the reactants and the conditions, two molecules of phenol react with one of the aldehyde. The type



of condensation lends itself to continuation, with the resulting production of polymers, and forms the basis for the preparation of the phenol-formaldehyde resin Bakelite (Belgian-born Leo H. Baekeland, 1909). Phenol condenses with formaldehyde with introduction in *ortho* and

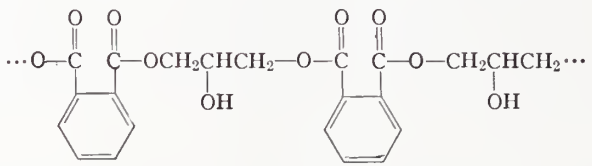


Bakelite resin

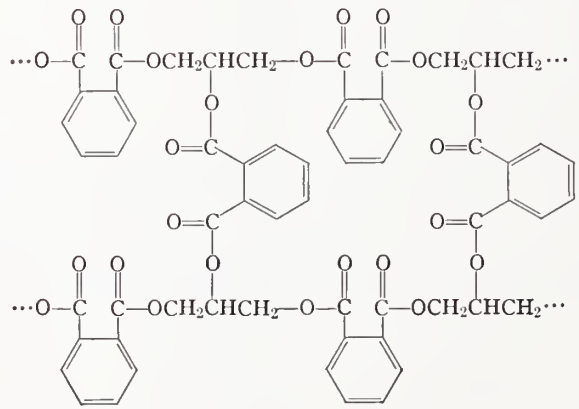
para positions of the methylol group, —CH_2OH, which condenses with another molecule of phenol with loss of water and production of a methylene bridge. Further polymerization results in a three-dimensional molecule of the type illustrated at the bottom of the preceding page.

19.28 Bakelite molding powder is made from material in an intermediate stage of three-dimensional polymerization. The powder is mixed with a filler to improve strength, and with small amounts of a plasticizer and a lubricant, and the mixture is put into a mold and cured by heating under pressure. A hard, durable Bakelite casting results.

19.29 **Alkyd Resins.** — These resins are so named because they result from condensation of a polyhydroxy alcohol with the anhydride of a dibasic acid (alcohol + acid = alkyd). The most common member, a glycerol-phthalic polymer, is called glyptal resin. The resinification process is believed to involve initial esterification of the two primary alcoholic groups of glycerol to form a linear polymer and then esterification of the secondary group with formation of cross links between the chains to produce a three-dimensional structure. Alkyl resins



Glyptal resin



are used primarily as coating materials, the largest single outlet of synthetic resins, but are also valuable as cements and binders.

19.30 **Synthetic Polymers in the Laboratory.** — An idea of the growing use of materials produced by modern techniques of polymerization will be afforded by consideration of items of equipment shown in

some of the photographic illustrations of this book. Ping-pong balls, used for photograph 2.5 as supplements to Sargent Co. molecular models for representing chlorine atoms, are made of celluloid. The odor of camphor is evident when a cut is made in a ball, and the nitrocellulosic character of the material is apparent when a piece is burned. The electric plug making connection to a hot plate (4.5) is made of Bakelite, as is the knob of a variable resistor used to control the speed of a stirring motor (4.18), the screw caps for bottles of non-corrosive chemicals (4.18), and the screw nuts securing the jacket to the inner tube of a Liebig-type condenser (9.5b; West condenser). Screw caps for bottles of du Pont sulfuric acid (3.8a), hydrochloric acid (6.23c), and nitric acid are made of a special grade of chemically resistant polystyrene.

Celluloid

Bakelite

Polystyrene

19.31

The tape used to seal the Bakelite caps of bottles of potassium permanganate and cyclohexene (4.18) is applied in the form of a ring of viscose tape so swollen by the water that it slips on easily; the tape on drying shrinks to form a tenacious cellophane film. Cellophane tape, used to secure a steel scorer to the osmium tetroxide container (4.10a), is made of cellophane with a rosin-rubber adhesive applied to one surface.

Cellophane

19.32

Durable Neoprene rubber is the material used for making filter adapters (4.19a,b) and rings for supporting round-bottomed flasks (12.17d). Plastic parts not visible in the photograph of a rotating evaporator (5.11) include Neoprene rings and a special, vacuum-tight Teflon seal through which the rotating shaft operates. Tygon tubing was chosen to carry water from the tap to an inverted Büchner funnel (5.11) because it makes the water-front visible. The Plas-Tex ice bucket (5.12a) is made of unbreakable polyethylene and is insulated with Fiberglas. Polyethylene is also the material of which the two-piece Büchner funnel (4.19b) is made. The Spongex ice buckets (4.18, 6.23b) are made of synthetic Hycar rubber.

Neoprene rubber

Teflon

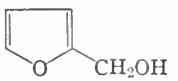
Plasticized polyvinyl chloride

Polyethylene

Butadiene-acrylonitrile copolymer

19.33

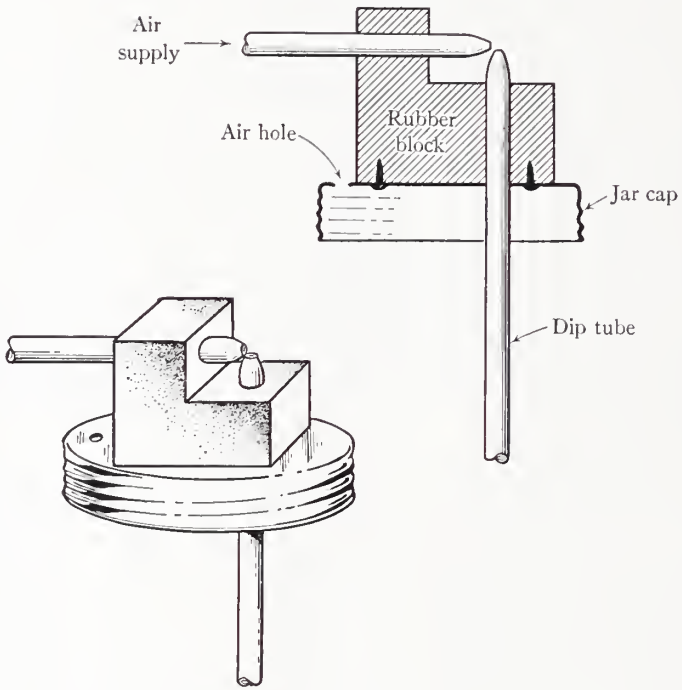
The wooden bench shown in photograph 9.5a is surfaced with Duralon 36, a thermosetting resin. The monomer, furfuryl alcohol, is polymerized by heat in the presence of an acidic catalyst; the polymer is probably a three-dimensional type resembling Bakelite. The old paint on the bench was removed with a sander and the clean wood surface sprayed with monomer, which was then polymerized in place by the heat from a battery of reflector drying lamps. At the time the photograph was taken, the resin had withstood ten years of attrition from acids, bases, hot flasks, dry ice, and solvents, none of which even soften the surface. The bench is cleaned by alternate washing with acetone and with soap and water.



Furfuryl alcohol

Plastic bench finish

19.34——— The cover of a book, particularly one used in a chemical laboratory, can be made waterproof, and is generally protected, by two or three applications of a clear plastic finish such as one of those available in convenient spray cans. A finish can be made easily from polymer and solvent and can be applied with a brush or with a spray gun constructed as shown in the drawing. A suitable formulation for the



Laboratory spray gun

dope is: 300 g. of B. F. Goodrich Chemical Company's vinyl resin Geon 400 × 110, 500 ml. butanone-2, 750 ml. 4-methylbutanone-2.

SUMMARY

Cellulose a condensation polymer formed from the monomer glucose by elimination of water between successive units of the cyclic β-form. Proteins are condensation polymers of α-amino acids of varying side chain.

Natural rubber an addition polymer of isoprene resulting from multiple 1,4-addition. Structure established by ozonization to levulinic aldehyde. X-ray analysis shows the configuration to be all-*cis*. Aging due to allylic air-oxidation to a hydroperoxide and eventual clipping of the chain with decrease in molecular weight. Latex, from rubber tree, an emulsion of rubber hydrocarbon in water stabilized by a protein; has special uses, e.g. for balloons, sponge rubber. The bulk of plantation latex is coagulated to raw rubber, which is vulcanized (heat with S, cross linking) for improvement of properties.

Synthetic rubbers. Early German Buna rubber (butadiene, polymerized with sodium). Emulsion polymerization made possible production of copolymers. Synthetic rubber for tires, GRS rubber, a copolymer of butadiene and styrene ($C_6H_5CH=CH_2$). Perbunan, or Hycar, rubber a copolymer of butadiene with acrylonitrile ($CH_2=CHCN$).

Neoprene rubber. Acetylene ⟶ vinylacetylene ⟶ chloroprene ⟶ polychloroprene ⟶ neoprene rubber (vulcanized). A 1,4 head-to-tail polymer, as established by oxidation. Shown by X-ray analysis to be all-*trans*.

Mechanism of polymerization of chloroprene. Benzoyl peroxide an initiator because it decomposes to phenyl and benzoate radicals (and CO_2). Radical initiator adds monomer units to form polymeric radicals. Chain eventually terminated by combination of two polymeric radicals to form polychloroprene.

Cellulose derivatives. Artificial silk by the nitrocellulose process: cellulose dinitrate (pyroxylin) solution in alcohol-ether extruded through a die, solvent evaporated, fiber denitrated. Celluloid: nitrocellulose plasticized with camphor (made of two isoprene units; cyclohexane ring in boat conformation locked by a bridge). Nitrocellulose lacquer: pyroxylin partially depolymerized to decrease viscosity of butyl acetate solution. Acetate rayon: cellulose acetate (di) dissolved in acetone, extruded to fiber, solvent evaporated. Viscose rayon: cellulose $\longrightarrow$ alkali cellulose $\longrightarrow$ ($+ CS_2$) cellulose xanthate, $-OC(=S)SNa$. Viscous solution in water extruded into bath of acid to produce a thread of regenerated cellulose. Cellophane: viscose sirup extruded through a slit and the sheet plasticized with glycerol.

Nylon: a polyamide fiber made by condensation polymerization of adipic acid and hexamethylenediamine. Adipic acid from phenol, via cyclohexanol and cyclohexanone. Hexamethylenediamine from adipic acid diamide by dehydration to the dinitrile and hydrogenation. Resemblance of nylon to fibroin (silk).

Dacron, a polyester fiber from terephthalic acid and ethylene glycol.

Polyethylene plastic, by free-radical induced polymerization of ethylene. At high pressures and temperatures (old process) chains are highly branched. Low-pressure process uses special catalyst (Ziegler) which gives superior plastic of greater linearity. Stereospecific polymer from propylene: a given chain all *d* or all *l*. "Synthetic natural rubber": isoprene with Ziegler catalyst gives all *cis*-1,4-polyisoprene.

Vinyl polymers (linked head to tail). Tygon (translucent, rubberlike, used for tubing): polyvinyl chloride plasticized with dioctyl phthalate (from 2-ethylhexanol-1, made by an aldol condensation). Vinyon fiber: copolymer of vinyl chloride and vinyl acetate. Polystyrene, from the monomer $C_6H_5CH{=}CH_2$, a thermoplastic. Methacrylate plastic (Plexiglas, Lucite); monomer methyl methacrylate made from acetone cyanohydrin. Teflon (superior resistance; gaskets), from the monomer $CF_2{=}CF_2$. Orlon fiber: polyacrylonitrile ($CH_2{=}CHCN$) dissolved in dimethylformamide and extruded.

Bakelite: three-dimensional phenol-formaldehyde resin.

Alkyd resins by condensation polymerization of glycerol with phthalic anhydride (glyptal resin). Primary alcoholic groups of glycerol react to give a chain polymer, the secondary group then reacts to form cross links.

Synthetic polymers in the laboratory. Identification of ten polymers appearing in illustrations of this book.

PROBLEMS

1. Isoprene can be made by the addition of acetylene to acetone (catalyzed by powdered KOH), selective hydrogenation (1 mole H_2), vapor-phase dehydration over alumina. Formulate the process.
2. Review methods cited earlier in the book for the production of the following monomers employed in the manufacture of synthetic elastomers: 2,3-dimethylbutadiene-1,3, butadiene, acetylene, chloroprene, styrene, acrylonitrile.
3. Butyl acetate, required for production of nitrocellulose lacquers, is made from a mixture of butyl alcohols produced as a petrochemical. Review the method by which the mixture is prepared.
4. For the production of cellulose acetate rayon fiber, the preferred material is the diacetate resulting from complete acetylation of cellulose to the triacetate and partial hydrolysis to remove one acetyl group. Fiber made from this material (A) is superior to that made from the diacetate (B) resulting from partial acetylation of cellulose. The difference must be that A contains more free hydroxyl groups that are easily acetylated, and whose esters are easily hydrolyzed, than does B. Examine the formula of cellulose (19.1) and identify these more reactive alcoholic groups.
5. Review methods available for production of the following monomers: ethylene, propylene, vinyl acetate, vinyl chloride, methyl methacrylate.
6. (*a*) Which of the monomers mentioned in questions 2 and 5 are available as petrochemicals?
   (*b*) Which can be obtained from acetylene?
   (*c*) Could butadiene be made from acetylene?

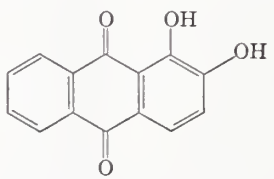
CHAPTER 20

DYES

20.1 **Natural Dyes.** — To be useful as a dye, a suitably colored compound must possess adequate stability to light and to the oxidizing action of chlorine in city water. Furthermore, the compound, if soluble in water, must have affinity for the fiber to be dyed so that it will be taken up from a hot aqueous dye bath; such a compound is a direct dye. If the colored compound is insoluble in water, some special mechanism must be available for applying dye to fiber. The natural dyes alizarin and indigo were known since antiquity and for centuries were nearly the only dyes used in substantial quantity. Neither is a direct dye.

20.2 Alizarin, 1,2-dihydroxyanthraquinone, occurs as a glycoside in the root of the madder plant. The pigment is soluble in water in the form of the sodium salt, but it does not adhere to either cellulosic

Alizarin, from madder root



Alizarin (m.p. 290°, b.p. 430°)

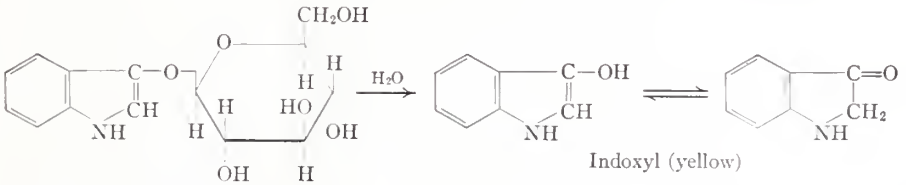
cotton fiber or to the protein fibers wool and silk. It is applied by processing the yarn in such a way that the fiber is impregnated with a mordant (L. *mordere*, to bite), a substance which adheres to the fiber and which is capable of binding the dye and of so linking it indirectly to the fiber. In a process which is actually more complicated than here described, yarn is soaked in aluminum sulfate solution and steamed to hydrolyze the sulfate to colloidal aluminum hydroxide. This mordanted cloth is then capable of taking up alizarin by forming a complex involving hydroxyl groups of both dye and mordant.

A mordant dye

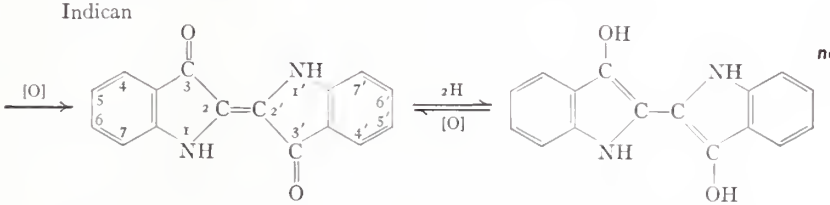
Alizarin dyes mordanted wool and silk, as well as mordanted cotton, in beautiful shades of red (Turkey Red dyeing).

20.3

Indigo is a brilliant and very fast blue dye obtained from the Indian plant *Indigofera*. The dye does not occur as such in the indigo plant but is derived from the colorless glucoside indican. On extraction of the crushed plant with water the glucoside is hydrolyzed



Indigo from a natural glycoside



by enzymes to glucose and indoxyl, and the latter is oxidized by air to the blue dye. Indigo is a high melting solid (m.p. 392°) completely insoluble in water, acids, or bases. It is applied to cotton by the process of vatting, which is reduction in the presence of alkali to colorless leucoindigo. Leucoindigo is enolic, or phenol-like, and hence dissolves in the alkaline solution to form a vat. When cotton fiber is immersed in the hot vat leucoindigo is adsorbed by hydrogen bonding and is not removed when the fiber is washed free of reducing agent. On exposure of the fiber to air, leucoindigo is oxidized to insoluble indigo and a very stable dyeing is obtained. Vat dyeing gives excellent results with cotton textiles, but the process is not applicable to wool and silk because the polypeptide links of the proteins are hydrolyzed in the hot alkaline dye bath and the fiber destroyed.

A vat dye

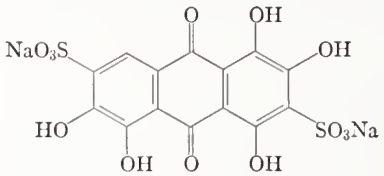
20.4

After the Kekulé benzene formula had become available as a guide to the study of aromatic compounds (1865), chemists of the period were stimulated to attempt elucidation of the structures of the two long-prized natural dyes with the idea that knowledge of the structures might open the way to synthetic production of the dyes themselves, and might also afford a pattern for the preparation of structurally related compounds for trial as dyes. Both objectives were achieved, chiefly by chemists of German universities and dye firms. The structure of alizarin was established by Graebe and Liebermann (1868), that of indigo by Baeyer (1883). Both dyes were

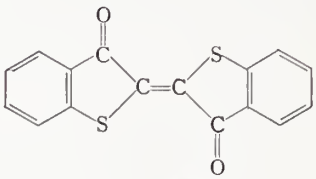
Structure and synthesis of the natural dyes

synthesized, and the processes were soon so perfected that synthetic alizarin and synthetic indigo of standard quality displaced the natural dyes. New polyhydroxyanthraquinones were synthesized and some of them were found applicable as mordant dyes, for example Alizarin Blue, WSR. Many variations of the indigo structure were explored,

Analogs of the natural dyes



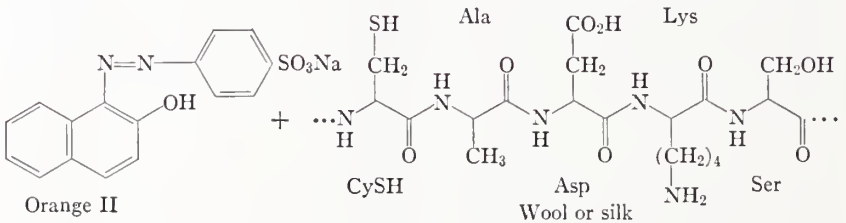
Alizarin Blue, WSR



Thioindigo

and some of the compounds proved satisfactory and were introduced as new indigoid vat dyes. Thioindigo, for example, is a fast, bluish red dye.

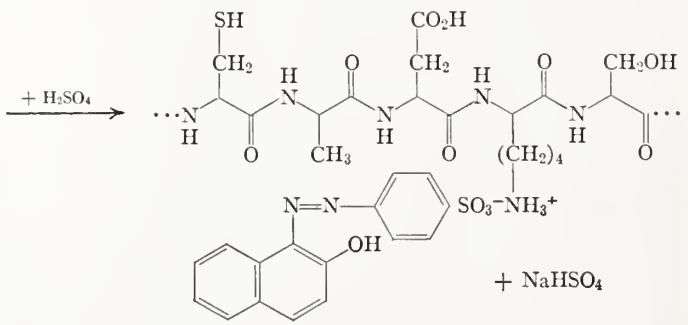
20.5 Azo Dyes. — Early in the history of the rapidly expanding dye industry, discovery by Peter Griess of the azo compounds opened the way to numerous easily prepared and brilliantly colored substances, and many of them proved satisfactory as dyes. Some are direct dyes for wool and silk; they are taken up from water solution when the protein fiber is heated in an acidified bath of dye because of the presence of a functional group capable of forming a salt linkage with a basic or acidic group of the protein. Orange II, a direct azo dye made by coupling β-naphthol with diazotized sulfanilic acid, can



Orange II

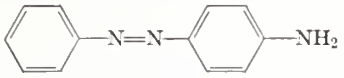
Wool or silk

Direct acid dye for wool and silk



combine with the ε-amino group of lysine units in the manner formulated, or with the basic guanidyl group of an arginine unit. The salt

linkage formed is stable because of the insolubility of the protein fiber in water. Aniline Yellow is a basic direct dye; it combines with free



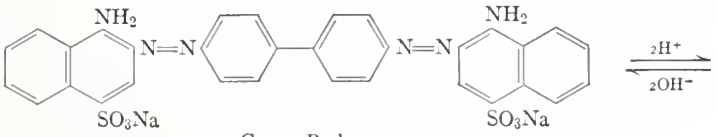
Aniline Yellow

Direct basic dye

carboxyl groups of units of aspartic and glutamic acid in the protein chain. The bright colors of these dyes are due to the azo group, —N=N—, which is called a chromophore (Gr. *chroma*, color, + *phoros*, bearer). Hydroxyl and amino groups, whose presence in a coupling component facilitates preparation of azo compounds, augment the function of a chromophoric group and are called auxochromes (Gr. *auxo-*, increase).

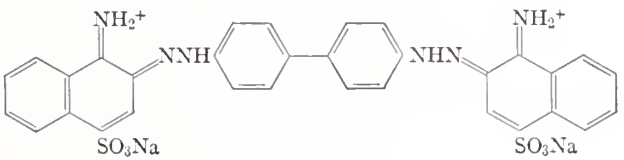
Orange II and Aniline Yellow have no affinity for the neutral cellulose chains of cotton and rayons. Dyes of a type known as substantive, however, are bound to cellulosic fibers by forces of adsorption or hydrogen bonding. An example is Congo Red, made by coupling doubly diazotized benzidine with naphthionic acid. This substance

20.6



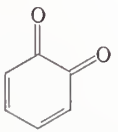
Congo Red

Substantive for cotton



Congo Blue

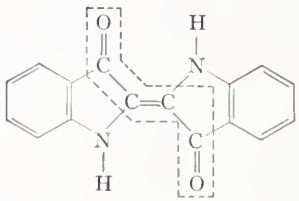
is associated in solution (mol. wt. about 8000) and its affinity for cotton is probably a consequence of the colloidal properties. It is now used as an indicator rather than a dye because the color changes from red to blue in the presence of mineral acid. Capture of two hydrogen ions is attended with redistribution of the double bonds. The red form, with the azo chromophores, thus gives place to a form in which the chromophoric groups are quinonoid; that is, they have the bond structure of an *ortho* quinone.

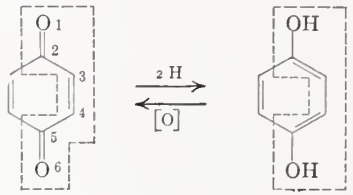


o-Benzoquinone

20.7 **Indanthrene.** — New vat dyes other than ones of indigoid structure were slow to be developed. Actually, the indigo molecule contains an enedione system (O=C—C=C—C=O) identical with that in quinone, and leucoindigo has a diene-diol system (HOC=C—C=C—OH) similar to that in hydroquinone. Quinones are characteristically colored,

Analogy to quinone

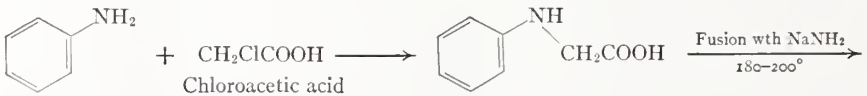




Quinone Hydroquinone

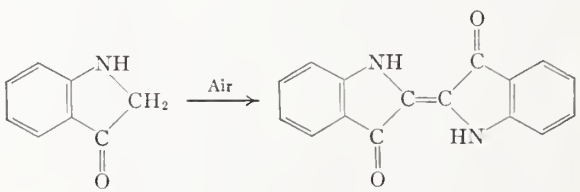
and hydroquinones, like leucoindigo, are colorless and soluble in alkali. The reduction of quinone to hydroquinone, which is rapid, quantitative, and reversible, involves 1,6-addition of hydrogen. With this information available, it is clear that a quinone of adequate color and stability might be applicable to cotton by vat dyeing just as indigo is applicable. Anthraquinones meet the requirement of intense color and stability, and anthrahydroquinones are particularly sensitive to air oxidation in alkaline solution.

20.8 However, the quinonelike character of indigo was not apparent to early dye chemists, and the first trial of a nonindigoid compound as a vat dye was the result of an accidental discovery made in 1901 by René Bohn of the Badische Anilin- und Soda-Fabrik. Bohn had done his research for the doctorate at the Institute of Technology at Zurich under Karl Heumann, who in 1890 had developed the first practical synthesis of indigo. The original process involving fusion



Aniline Phenylglycine

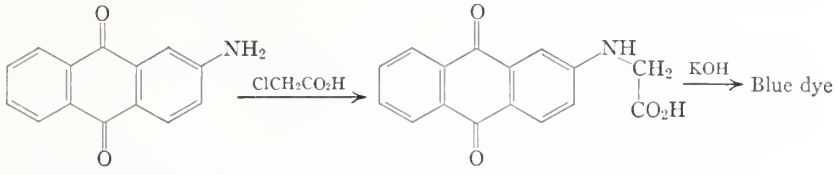
Heumann indigo synthesis



Indoxyl Indigo

of phenylglycine with alkali at 300° was later improved by the finding that the cyclization can be effected by the action of sodamide at a lower temperature with improvement of yield. Bohn, seeking a new dye, undertook to apply the Heumann synthesis to β-aminoanthra-

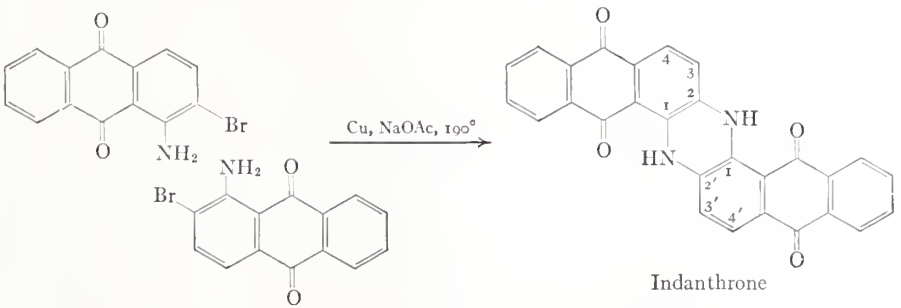
quinone in the hope of producing a derivative of indigo in which the two benzene rings are replaced by anthraquinone groups. He con-



β-Aminoanthraquinone

densed β-aminoanthraquinone with chloroacetic acid and attempted to close the ring by fusion with alkali. The end rings of anthraquinone are joined to two deactivating carbonyl groups and hence anthraquinone is substituted only with difficulty and at high temperatures. Nevertheless, under conditions sufficiently drastic to promote reaction Bohn obtained a blue compound having properties expected of a vat dye, and he consequently named it indanthrene (indigo of anthracene). The analytical results, however, did not correspond to the expected formula, and Bohn soon found that the dye is obtained by alkali fusion of β-aminoanthraquinone itself, reformed by cleavage of the CH_2CO_2H group. Yields of 48–50% are obtainable by fusion of the β-amino compound with potassium hydroxide and potassium nitrate (oxidizing agent) at temperatures of 150–200°. Bohn (1903) also obtained the blue dye by heating 1-amino-2-bromoanthraquinone in nitrobenzene solution (190°) with condensing agents, and recognized the substance as having a condensed-ring system. The synthesis from the bromoamine established the structure. Indanthrene, which

Indanthrene (in U.S., "indanthrone")



Indanthrone

proved to be a vat dye of superior fastness, is thus an anthraquinone derivative insoluble in water and applicable as a vat dye by conversion to the alkali-soluble hydroquinone. Many other anthraquinonoid vat dyes of superior quality are now available.

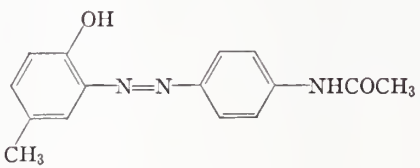
Hydrophobic Fibers. — Rayon and other fibers composed of regenerated cellulose can be dyed with standard cotton dyes with little modification. Nylon can be dyed with acidic dyes developed for wool

20.9

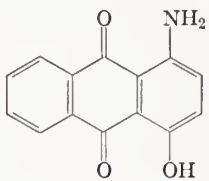
and silk because the polyamide chains contain enough terminal amino groups to bind acidic dye molecules by salt formation. Cellulose acetate, as well as the purely synthetic fibers Dacron (polyester), Vinyon (vinyl acetate-chloride copolymer), and Orlon (polyacrylonitrile), confronted dye manufacturers with a new problem. These are neutral materials described as hydrophobic fibers, or water-repellent. They either lack hydroxyl groups entirely, or have too few such groups (cellulose acetate) for hydrogen bonding of a substantive azo dye or of the leuco form of a vat dye. Indeed the hydrophobic fibers are indifferent to the usual cotton dyes as well as to dyes for wool and silk. Investigation both of new dye types and of dyeing techniques eventually led to the development of a method in which the hydrophobic fiber is dyed from a hot aqueous emulsion of a water-insoluble dye in the presence of a dispersing agent, when the dye apparently enters the fiber to form a solid solution. Dyes with affinity for hydrophobic fibers under these conditions are compounds of relatively low molecular weight containing free hydroxyl or amino groups. Typical dyes of this group are the azo compound Fast Yellow G and the anthraquinone Celliton Fast Pink B. Although all hydrophobic fibers can be dyed by substantially the same procedure, each requires specific adjustment of dye bath formulation and time of application. The dye manufacturer may be confronted not only with the problem

New dyes required

Satisfactory types



Fast Yellow G



Celliton Fast Pink B

of finding a procedure for dyeing each new synthetic fiber, but with the further obligation to provide enough dyes of the specific type required to cover the whole range of color and shade, so that they all can be applied by the same dyeing technique. With constant research leading to introduction of superior new products and retirement of old ones, the number of dyes that are, or have been, on the market is estimated as at least 1500.

Multiplicity of dyes

SUMMARY

Alizarin and indigo, long-known natural dyes, applied by indirect methods since the former has no affinity for fiber and the latter is insoluble in water.

Alizarin (1,2-dihydroxyanthraquinone) from madder root applied to yarn treated with colloidal aluminum hydroxide mordant, which binds dye to fiber. Applicable as mordant dye to wool and silk as well as cotton.

Indigo from the glucoside indican present in an Indian plant. Enzymatic hydrolysis splits off glucose and gives indoxyl, which on air oxidation

yields indigo. A vat dye: reduction in alkaline solution ($Na_2S_2O_4$) gives solution of leucoindigo: this adheres to cotton by hydrogen bonding and on exposure to air is oxidized to indigo.

Problems of structure and synthesis solved; synthetic dyes displaced natural dyes; new dyes developed by synthesis of analogs.

Azo dyes. Orange II direct to wool and silk because $—SO_3^-$ forms salt linkages with lysine and arginine units of the proteins. Aniline Yellow: a direct basic dye, since $—NH_2$ combines with carboxyl group of aspartic and glutamic acid units. Congo Red, a substantive dye for cotton, adsorbed by hydrogen bonding, made from benzidine and naphthionic acid, turns blue with acid due to change from azo chromophore to a quinonoid chromophore.

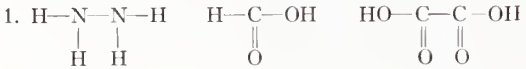
Indanthrene. Analogy of indigo and leucoindigo to quinone and hydroquinone not recognized, and the first trial of a quinone as a vat dye due to a chance observation. Heumann had synthesized indigo from aniline; his student Bohn applied the synthesis to β-aminoanthraquinone hoping to obtain the indigo of anthracene. The product, a superior vat dye, proved to be an anthraquinone of a new type.

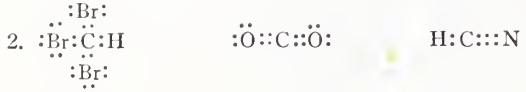
PROBLEMS

1. Formulate all the reactions required for the preparation of Orange II starting with benzene and naphthalene.
2. How are the intermediates for Congo Red prepared (benzidine and naphthionic acid)?
3. (*a*) Would you expect anthraquinone to enter into Friedel-Crafts reaction with acetyl chloride and aluminum chloride?
   (*b*) Can the direction of mononitration and monosulfonation of anthraquinone be predicted?
   (*c*) β-Aminoanthraquinone is prepared by the reaction of anthraquinone-β-sulfonate with ammonia. Comparable reactions cannot be realized with sulfonates of anthracene, naphthalene, or benzene. Can you think of an analogous displacement which would serve to clarify the reaction?

ANSWERS TO PROBLEMS

CHAPTER 1. NATURE OF ORGANIC COMPOUNDS

1. 

2. 

3. CH_3CHBr_2 and $BrCH_2CH_2Br$; CH_3CBr_3 and $BrCH_2CHBr_2$

4. No; C_3H_7I could be either $CH_3CH_2CH_2I$ or CH_3CHICH_3

5. $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3CH_2OCH_3$. The third formula is correct.

6. $CH_3CH_2CH_2CH_2CH_2CH_2Cl$;
$CH_3CH_2CH_2CH_2CHCH_3$; $CH_3CH_2CH_2CHCH_2CH_3$
(Cl) (Cl)

7. Possible formulas: $C_{10}H_{22}O$, $C_{14}H_8O_4$, $C_{21}H_{31}O_3N$, $C_{20}H_{32}OSN_2$

CHAPTER 2. STRUCTURES OF ALIPHATIC COMPOUNDS

1. Dibromoisobutanes:
$(CH_3)_2CHCHBr_2$ (1,1-), $(CH_3)_2CBrCH_2Br$ (1,2-), $BrCH_2CH(CH_3)CH_2Br$ (1,3-)
Dibromo-*n*-butanes:
$CH_3CH_2CH_2CHBr_2$ (1,1-), $CH_3CH_2CHBrCH_2Br$ (1,2-), $CH_3CHBrCH_2CH_2Br$ (1,3-), $BrCH_2CH_2CH_2CH_2Br$ (1,4-), $CH_3CH_2CBr_2CH_3$ (2,2-), $CH_3CHBrCHBrCH_3$ (2,3-)

2. $(CH_3)_2CHCH_2CH_2CH_2CH_3$, 2-methylhexane
$(CH_3)_2CHCH_2CH(CH_3)_2$, 2,4-dimethylpentane
$(CH_3)_2CHCH(CH_3)CH_2CH_3$, 2,3-dimethylpentane
$CH_3CH_2CH(CH_3)CH_2CH_2CH_3$, 3-methylhexane
$(CH_3)_3CCH_2CH_2CH_3$, 2,2-dimethylpentane

3. (*a*) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CHClCH_2Br$
(*b*) $CH_3CH_2CH_2CH_2CHClCCl_2CH_3$
(*c*) $CH_3CH_2C(Br)(CH_3)_2$
(*d*) $(CH_3CH_2)_4C$

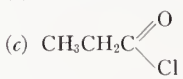
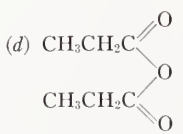
4. (*a*) 2,5-Dimethylheptane
(*b*) 2-Methylpropane
(*c*) 3-Methylhexane
(*d*) 2,5-Dimethyl-3-ethylhexane

5. 2,2-Dimethylhexane, $CH_3CH_2CH_2CH_2C(CH_3)_3$
3,3-Dimethylhexane, $CH_3CH_2CH_2C(CH_3)_2CH_2CH_3$
2,2,3-Trimethylpentane, $CH_3CH_2CH(CH_3)C(CH_3)_3$
2,2,4-Trimethylpentane, $(CH_3)_2CHCH_2C(CH_3)_3$

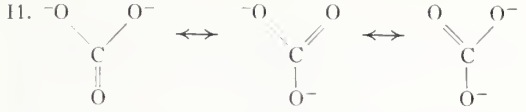
6. (*a*) Propanetriol-1,2,3
(*b*) 2,4-Dimethylhexanol-2
(*c*) 2,5-Dimethylheptene-3
(*d*) 4-Methylhexyne-1
(*e*) 2,5-Dimethylhexadiene-2,4
(*f*) 2-Methyl-3-isopropylhexene-5-ol-1
(*g*) 1,2-Dimethyl-4-ethylcyclohexane
(*h*) Cyclohexanedione-1,2

7. (*a*) $CH_3CH_2CH(CH_2CH_3)CH(CH_3)CH_2OH$
(*b*) $C_6H_5CH{=}CHCH{=}CHC_6H_5$
(*c*) $(CH_3)_2C{=}CHCH_3$
(*d*) $CH_3CH(OH)CH(OH)CH_3$
(*e*) $ClCH_2CH(CH_3)CH_2CH{=}CH_2$

8. 3-Methylhexanol-1
3-Methylhexanol-2
2-Ethylpentanol-1
3-Methylhexanol-3
4-Methylhexanol-3
4-Methylhexanol-2
4-Methylhexanol-1

9. (*a*) $CH_3CH_2COOCH_3$
(*b*) $CH_3CH_2COOCH(CH_3)_2$
(*c*) 
(*d*) 

10. There is no possibility for formation of a resonance-stabilized anion.

11. 

12. $CH_3CH_2CH_2CH_2CH_2OH$ $CH_3CH_2C(OH)(CH_3)_2$
$CH_3CH_2CH_2CH(OH)CH_3$ $(CH_3)_2CHCH(OH)CH_3$
$CH_3CH_2CH(OH)CH_2CH_3$ $(CH_3)_2CH_2CH_2OH$
$CH_3CH_2CH(CH_3)CH_2OH$ $(CH_3)_3CCH_2OH$

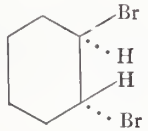
CHAPTER 3. REACTIONS OF ALIPHATIC HYDROCARBONS

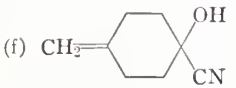
1. No. Since *n*-pentane is symmetrical, the two terminal methyl groups are identical and contain six hydrogens of one type available for substitution. The two next-to-the-end methylene groups contain four hydrogens of a second type, and the central methylene group contains two hydrogens of a third type. Hence the ratio expected statistically is 6:4:2.

2. $RCH_2CH_2\cdot + \cdot O{:}O\cdot + \cdot CH_2CH_2R \longrightarrow RCH_2CH_2{:}O{:}O{:}CH_2CH_2R$ (a peroxide)

3. (*a*) $(CH_3)_2CBrCHBrCH_2CH{=}CH_2$
(*b*) $CH_3CHBrCHBrCH_2C{\equiv}CCH_3$

4. (*a*) $BrCH_2CHBrCH_2Br$
(*b*) $(CH_3)_3CCHCH_3$ (OSO_2OH)
(*c*) $CH_3CHC(CH_3)CH_2CH_3$ (Br, OH) (*d*) $CH_3CHCH_2C(I)CH_3$ ($CH_2CH_2CH_3$)

(e) 

(f) 

(g) $CH_3CH{=}CHCH_2C{\equiv}C{-}C(CH_3)(CH_3)(OH)$

5. $CH_2{=}CHC{\equiv}CH + HOH \xrightarrow{\text{catalyst}} [CH_2{=}CHC(OH){=}CH_2] \xrightarrow{\text{2,4-shift}} CH_2{=}CHCCH_3$ (Methyl vinyl ketone) (O)

CHAPTER 4. OXIDATION AND REDUCTION

1. $CH_3CH_2CH(OH)CH_3$

2. $CH_3CH_2C(OH)(CH_3)_2$

3. (*a*) Positive. (*b*) Negative. (*c*) Negative [only *vic*-glycols (1,2-) are cleaved].

4. Both can be oxidized, but the initial oxidation product of (*a*) gives a positive silver mirror test while that of (*b*) gives a negative test. If (*a*) is oxidized with excess permanganate the product will respond to a test for an acid.

5. Only the *vic*-glycol (*a*) is cleaved by periodic acid.

6. The possibilities are the 2-acetate and the 4-acetate. On glycol cleavage with HIO_4, the 2-acetate is cleaved at the 3,4-position to give propionaldehyde (CH_3CH_2CHO) and the 4-acetate is cleaved at C_2–C_3 to give acetaldehyde. Hence identification of the aldehyde formed would establish the structure.

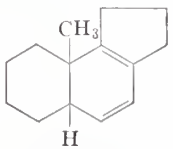
7. The amount of permanganate used was exactly that theoretically required. Theoretical yield, 23.0 g.; actual yield, 30.5% of the theoretical.

8. On exhaustive permanganate oxidation, (*a*) yields acetic acid and the diacid $HOOCCH_2COOH$ (malonic acid) and (*b*) yields CO_2 and the diacid $HOOCCH_2CH_2COOH$ (succinic acid).

9. (*a*) CO_2 + $HOOC(CH_2)_8COOH$ (sebacic acid)

(*b*) $(CH_3)_2C{=}O$ + $HOOCCH_2CH_2C(CH_3){=}O$ (levulinic acid) + HOOCCOOH (oxalic acid)

10. Number of rings = 14 − 10 − 2 + 1 = 3. Example of such a hydrocarbon:

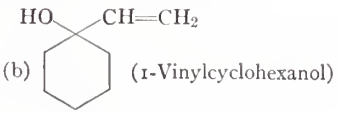


11. Hexene-2. Hexene-3 would meet the requirements except for the formation of two acids of the type RCOOH; it would yield two moles of CH_3CH_2COOH.

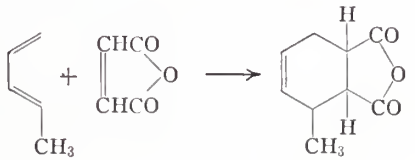
12. $CH_3CH_2C(CH_3){=}CHCH_2CH_2CH{=}CHCH_2CH_3$

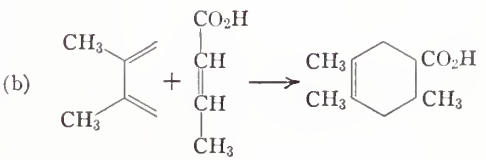
13. (*a*) $(CH_3)_2CHCH_2CH_2CH_2CH_2OH$
(*b*) $CH_3CH(OH)CH_2CH_2CH_2COOH$

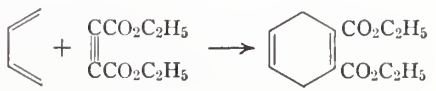
14. (*a*) $CH_3CH{=}CHCH_2CH{=}CHCH_3$

(*b*)  (1-Vinylcyclohexanol)

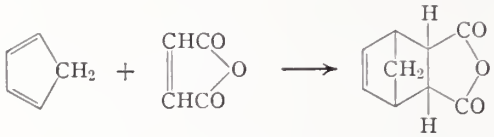
CHAPTER 5. CONJUGATED DIENES

1. (a) 

(b) 

(c) 

2. (*a*) λ_{max} 265 mμ
(*b*) The reaction proceeds well and gives a product with a cyclohexene ring spanned by a methylene bridge.



3.



4. Cyclohexadiene-1,4

5. Analogy to butadiene would lead to this prediction, which is borne out by experiment. The initial product of addition is $BrCH_2CH{=}CHCH{=}CHCH_2Br$.

CHAPTER 6. AROMATIC HYDROCARBONS

1. (*a*) 4-Nitro-1,3-dimethoxybenzene
(*b*) Substitution *ortho* to the acetylamino group (more potent)
(*c*) Substitution *ortho* to the methyl group (smaller)
(*d*) Substitution *ortho* to the methyl group and *meta* to $-COCH_3$
(*e*) Mild conditions: 2-nitrophenol-4-sulfonic acid; more drastic conditions: 2,4-dinitrophenol, picric acid
(*f*) 2,4,5-Trimethylacetophenone
(*g*) 2,4-Dichloronitrobenzene
(*h*) $C_6H_5COCH_2C_6H_4(p)$-$COCH_2CH_2CO_2H$
(*i*) *o*- and *p*-$NO_2C_6H_4CH_2C_6H_4CO_2H(p)$
(*j*) 4-$ClC_6H_4CH_2C_6H_4CH_3$-4′
(*k*) 4-Methyl-3′-nitro-4′-hydroxydiphenyl

2. (*a*) Benzene, *t*-butyl chloride, with 0.4 mole $AlCl_3$
(*b*) Condensation of *t*-butyl chloride with *t*-butylbenzene in the presence of $AlCl_3$ at 25°

3. $(CH_3)_3CCl + C_6H_5CH_3$ $(+ AlCl_3) \longrightarrow$ *p*-$(CH_3)_3CC_6H_4CH_3$; the *t*-butyl group is resistant to oxidation (no α-H to be attacked), and hence the hydrocarbon can be oxidized to the acid desired.

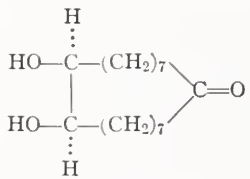
4. The ring carrying the nitro group is deactivated, and hence oxidation gives 3-nitrophthalic acid.

5. $C_6H_5C(OH)(CH_3)_2$

CHAPTER 7. CYCLOALKANES

1. Pentene-2 and 1,2-dimethylcyclopropane would decolorize bromine solution whereas cyclopentane would not. Pentene-2, but not 1,2-dimethylcyclopropane, would give a test for unsaturation with permanganate.

2.



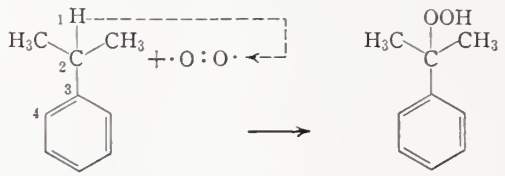
3. All the ethane units in cyclopentane are exactly like the 2,3- and 5,6-units of the boat form of cyclohexane, and hence the hydrogen–hydrogen distances are all 2.33 Å. In chair-cyclohexane the maximal approach of hydrogens is 2.50 Å. Thus greater H–H repulsion accounts for the relative instability of cyclopentane.

4. The *trans*-isomer can have only one conformation, and in this one methyl is equatorial and the other is axial. For the *cis*-isomer, diaxial and diequatorial forms are both possible and hence, in the more stable diequatorial form, the *cis*-isomer is more stable than the *trans*-isomer.

CHAPTER 8. PETROLEUM

1,2. The C_4-cut contains *n*-butane and isobutane; on cracking, the isobutane is converted largely into isobutene, which dimerizes under the catalytic influence of sulfuric acid to form isooctene, of high octane rating. The amount of isobutane initially present in the C_4-cut is substantially increased by isomerization of *n*-butane under catalysis by $AlCl_3$.

3. The α-hydrogen of the cumene side chain is activated by the benzene ring and can add to one end of the diradical oxygen molecule to form the hydroperoxide.



CHAPTER 9. ACIDS AND BASES

1. The benzoic acid utilized was 48.6 g.; the theoretical yield is $48.6 \times 136.14 \div 122.12 = 54.2$ g.; actual yield 95.0%.

2. The isolation procedure is satisfactory since the phenolic group of the ester, *o*-$HOC_6H_4CO_2CH_3$ (oil of wintergreen), is not acidic enough for the substance to be extracted by bicarbonate. The esterification procedure is satisfactory except that the reflux period should be extended, since the *o*-hydroxyl group exerts a blocking effect (steric hindrance) and slows down attainment of equilibrium. Thus comparative esterifications by the procedure of paragraph 9.5 gave the following results:

	Reflux period	*Ester formed**	*Acid recovered*
BENZOIC ACID	2 hrs.	92.2%	2.8%
BENZOIC ACID	5 hrs.	92.4%	2.6%
SALICYLIC ACID	2 hrs.	67.8%	27.2%
SALICYLIC ACID	16 hrs.	89.3%	4.7%

3. Water adds to give acetic acid; ammonia adds analogously to give acetamide, CH_3CONH_2.

4. Maleic acid, pK_a 1.9 (compare fumaric acid, pK_a 3.0): proximity of the two carboxyl groups enhances the inductive effect of one on the other.

5. $CN > Cl > Br > I > CH_3O > SH > OH > C_6H_5$

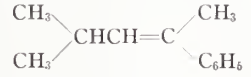
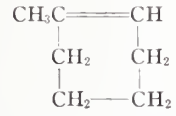
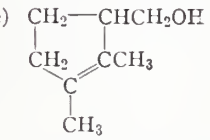
* Percent of the theoretical amount without allowance for the acid recovered.

6. No; the basic amino group accepts the hydroxylic hydrogen to give an inner-salt structure:

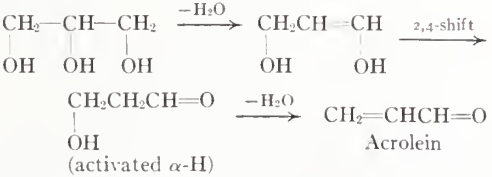
$$CH_3CHCOO^-$$
$$\quad\;|$$
$$\quad NH_3^+$$

7. (*a*) *p*-$CH_3OC_6H_4CO_2H$
(*b*) $CH_3CONHCH_2CO_2H$
(*c*) *o*-$HOOCC_6H_4CONH_2$

CHAPTER 10. ELIMINATION REACTIONS

1. (*a*) $C_6H_5CH_2CH_2CH{=}C(CH_3)_2$
(*b*) $CH_3CH{=}CHCH{=}CHCH_3$
(*c*)

(*d*)

(*e*)


2. (*a*) $C_6H_5CH{=}CHCH_2CH_3$
(*b*) $CH_3CH_2C{\equiv}CCH_2CH_3$
(*c*) $C_6H_5CH{=}CHCH{=}CHC_6H_5$
(*d*) $CBr{\equiv}CBr$

3.


4. $C_6H_5CH{=}CH_2 + Br_2 \longrightarrow$
$C_6H_5CHBrCH_2Br \longrightarrow C_6H_5C{\equiv}CH$ (alc. KOH)

5. The carbonyl group of I was hydrogenated (like an ethylenic double bond), and the alcohol II was dehydrated to III. The nitrogen bridge had to be eliminated, and Willstätter decided to do this by a sequence of two Hofmann degradations, for two additional double bonds could be introduced in the process. The tertiary base III was methylated to give the quaternary ammonium iodide, which was transformed into the hydroxide IV. Pyrolysis severed one carbon–nitrogen bond in an elimination of water involving a hydrogen β- to the bond severed and activated by the double bond already present; the product formed, V, contains a conjugated diene system. By a second Hofmann degradation, nitrogen was finally eliminated as trimethylamine, to give the conjugated cyclooctatriene VI. Selective bromination with just one mole of bromine proceeded with addition of bromine to the two ends of the triene system to give VII. This 1,6-addition is analogous to a 1,4-addition to a diene. One of the three double bonds was thereby sacrificed, but when the dibromide VII was treated with trimethylamine, followed by silver hydroxide, the product VIII was a di-quaternary ammonium hydroxide which on pyrolysis supplied two new double bonds and gave the desired cyclooctatetraene IX. During World War II, the German industrial chemist W. Reppe discovered a one-step synthesis of IX: polymerization of acetylene under pressure in the presence of a nickel catalyst.

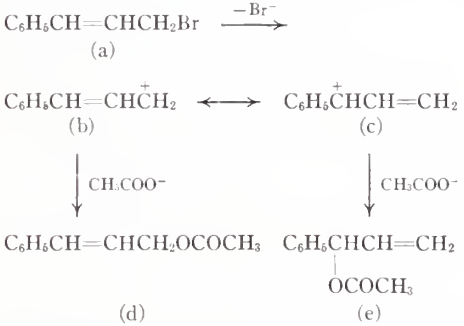
6. On dehydration to a diene, followed by chromic acid oxidation, the first diol would give a C_6-diketone and the second would give a C_6-diacid.

CHAPTER 11. REPLACEMENT REACTIONS

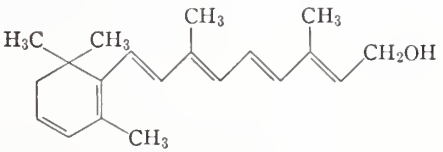
1. (*a*) $NaOCH_3$
(*b*) Moist silver oxide (AgOH)
(*c*) Concd. hydrochloric acid
(*d*) Concd. hydrochloric acid
(*e*) PCl_3

2. Zerewitinoff determination would show four active hydrogens before acetylation and only two after acetylation. Oxidation would yield a substance giving a negative silver mirror test, hence primary alcoholic groups are excluded.

3. Cinnamyl bromide (a) is of the allylic type and must initially dissociate to the ion (b). This is in resonance with ion (c), and combination of the two ions with acetate ion should give rise to the isomers (d) and (e).



4. Cracking: ethylbenzene $\longrightarrow$ styrene (6.22); $CH_3CH_3 \longrightarrow CH_2{=}CH_2$ (8.10); $(CH_3)_2CHCH_3 \longrightarrow (CH_3)_2C{=}CH_2$ (8.10); $2\,CH_4 \longrightarrow CH{\equiv}CH$ (8.18); C_7-petroleum hydrocarbons $\longrightarrow$ toluene (8.17). Pyrolysis of acetone to ketene (9.6). Thermal dehydration of alcohols over alumina (10.3). Alkenes from alkylsulfuric acids (10.4). $ClCH_2CH_2Cl - HCl$ (thermal) $\longrightarrow CH_2{=}CHCl$ (10.11). Thermal decomposition of quaternary ammonium hydroxides to alkenes (Hofmann degradation, 10.12).

5.

Vitamin A_2

The scheme of synthesis that comes to mind is allylic bromination of vitamin A_1 with N-bromosuccinimide, and dehydrohalogenation. The high reactivity of the allylic alcohol group, however, introduces a complication. The synthesis achieved by E. R. H. Jones in England in 1951 thus utilized vitamin A_1 acid, which has a carboxyl group in place of $-CH_2OH$; after allylic bromination and elimination of HBr, the synthesis was completed by the transformation $-COOH \longrightarrow -CH_2OH$ by a method described in Chapter 12.

6. (*a*) $p\text{-}NO_2C_6H_4NH_2 \xrightarrow{HCl,\ NaNO_2} [p\text{-}NO_2C_6H_4\overset{+}{N}{\equiv}N]Cl^- \xrightarrow{Cu_2Cl_2} p\text{-}NO_2C_6H_4Cl \xrightarrow{3\ SnCl_2,\ 6\ HCl} p\text{-}NH_2C_6H_4Cl \xrightarrow{HCl,\ NaNO_2} Cl^-[N{\equiv}N^+C_6H_4Cl\text{-}p] \xrightarrow{Cu_2Br_2} BrC_6H_4Cl\text{-}p$

(*b*) $p\text{-}CH_3C_6H_4NH_2 \xrightarrow{HCl,\ NaNO_2} [p\text{-}CH_3C_6H_4N^+{\equiv}N]Cl^- \xrightarrow{Cu_2(CN)_2} p\text{-}CH_3C_6H_4CN \xrightarrow{Hydrol.} p\text{-}CH_3C_6H_4CO_2H \xrightarrow{Oxid.} p\text{-}HO_2CC_6H_4CO_2H$

(*c*) *o*-Toluidine $\xrightarrow{HCl,\ NaNO_2} [o\text{-}CH_3C_6H_4N^+{\equiv}N]Cl^- \xrightarrow{Hydrol.} o\text{-}CH_3C_6H_4OH \xrightarrow{Br_2}$ 2,4-dibromo-*o*-cresol

7. Dinitration of chlorobenzene gives 2,4-dinitrochlorobenzene, in which the halogen is labile; condensation with methylamine and reduction gives the product desired.

CHAPTER 12. REACTIONS OF CARBONYL COMPOUNDS

1. (*a*) $CH_3CH_2CH_2MgBr + (CH_3)_2CO$
(*b*) $2\ CH_3CH_2CH_2MgBr + CH_3CO_2C_2H_5$
(*c*) $CH_3CH_2CH_2MgBr + CH_2O$
(*d*) $CH_3CH_2CH_2MgBr +$ ethylene oxide
(*e*) $CH_3CH_2CH_2MgBr + CH_3COCH_2CH_3$

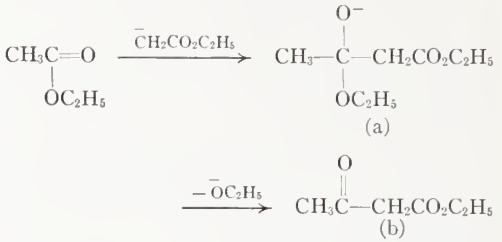
2. Ethylene oxide must owe its reactivity to strain resulting from distortion of the normal valence angles of both oxygen and carbon in the three-membered ring. The analogy to cyclopropane suggests that the normal angle of the valence bonds of oxygen must be about the same as the normal angle between carbon valences (109° 28′). X-ray analyses have established that in dimethyl ether the valences of oxygen extend at an angle of 111°.

3. Since in acetophenone, $C_6H_5COCH_3$, the phenyl group, by a resonance effect, decreases the additive power of the carbonyl group, benzaldehyde can be expected to be less reactive than its hexahydro derivative.

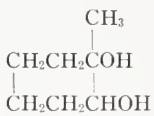
4. Positive: *b*, *e*, *g*

5. Vinylcyclopentane

6. Reaction of ethyl acetate with ethoxide ion to form $\bar{C}H_2CO_2C_2H_5$, addition of this anion to the carbonyl group of another molecule of ethyl acetate to form the anion (a), and expulsion of ethoxide ion to form (b).

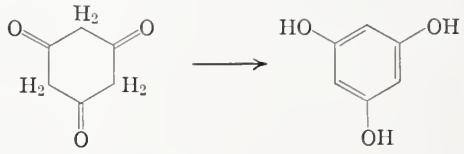


7. $HOCH_2CH_2CN$
8. $(CH_3)_2CHCH(OH)CH_3$
9. $CH_3COCH_2CH_2CHO$
10. The formation of a monoacetate indicates the presence of a primary or secondary alcoholic group; resistance to phenylhydrazine shows that the second oxygen atom is not present as a carbonyl group. The reaction with periodic acid is evidently a glycol cleavage producing two carbonyl groups; since these are in the same molecule, III, the glycol group must be part of a ring. The positive Fehling's test indicates that at least one carbonyl must be present as an aldehydic group, and the formation of iodoform reveals the presence of a methyl ketone group. The acid $HOOC(CH_2)_4COOH$ must, then, have come from the keto aldehyde $CH_3CO(CH_2)_4CHO$, and the glycol I must have the structure:

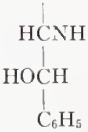


11. On chlorination in the presence of a trace of iodine catalyst, (*a*) would give a monochloro derivative, (*b*) would give a dichloro derivative, and (*c*) would remain unchanged.

12. The initial product of hydrolysis, I, enolizes to phloroglucinol, II, because the latter is an aromatic compound stabilized by resonance.



I II

13. 
Ephedrine

Synthesis

(*a*) $C_6H_5COCH_2CH_3 \xrightarrow{Br_2} C_6H_5COCHBrCH_3 \xrightarrow{CH_3NH_2} C_6H_5COCH(NHCH_3)CH_3$; reduction.

(*b*) $C_6H_5CHO + CH_3CH_2NO_2 \longrightarrow C_6H_5CHOHCH(NO_2)CH_3 \longrightarrow C_6H_5CHOAcCH(NO_2)CH_3 \longrightarrow C_6H_5CHOAcCH(NH_2)CH_3 \longrightarrow C_6H_5CHOAcCH(NHCH_3)CH_3$; hydrolysis

CHAPTER 13. SYNTHESIS

1. (*a*) $(CH_3)_2CHMgBr + CH_2O$
(*b*) $(CH_3)_2CO + BrMgCH_2CH_3$
(*c*) $CH_3CH_2CO_2CH_3 + 2\ CH_3CH_2MgI$
(*d*) $CH_3CH_2CH_2MgBr$ + ethylene oxide
(*e*) $CH_3CH_2MgCl + OC(CH_3)_2$; dehydration
(*f*) $(CH_3)_2CHMgBr$ + ethylene oxide $\longrightarrow$ $(CH_3)_2CHCH_2CH_2OH$;
$(CH_3)_2CHCH_2CH_2MgBr + CH_2O$; dehydration
Shorter synthesis: $(CH_3)_2CHMgBr + BrCH_2CH{=}CH_2$
(*g*) $(CH_3)_2CHMgI + OC(CH_3)_2$; dehydration
(*h*) $(CH_3)_2CO + CH_3MgCl$; dehydration; hydrogenation
(*i*) $CH_3CH_2CH_2MgBr + OC(CH_3)_2$; dehydration; hydrogenation
(*j*) $2\ (CH_3)_2CHMgBr + CH_3CO_2C_2H_5$; dehydration; hydrogenation

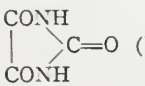
2. (*a*) $2\ CH_3CH_2CH_2MgBr + CH_3CH_2CO_2CH_3$; dehydration; hydrogenation
(*b*) $CH_2{=}CHCH_2MgBr + OC(CH_3)_2$; dehydration
(*c*) $(CH_3)_2CO + CH_3MgI \longrightarrow (CH_3)_3COH$;
$(CH_3)_3COH \longrightarrow (CH_3)_3CBr \longrightarrow$
$(CH_3)_3CMgBr$; $(CH_3)_3CMgBr + CH_2O \longrightarrow$ $(CH_3)_3CCH_2OH$

3. (*a*) $(CH_3)_2CHCH_2MgCl + OC(CH_3)_2$; dehydration
(*b*) $CH_3CH_2CH(OH)CH_3 \longrightarrow CH_3CH_2COCH_3$; reaction with $CH_3CH_2CH_2MgBr$
(*c*) $(CH_3)_2CO + CH_3CH_2CH_2CH_2MgCl$; dehydration; hydrogenation
(*d*) $(CH_3)_3CMgCl + CH_3CH_2CHO$; conversion to $(CH_3)_3CCHBrCH_2CH_3$; formation of RMgBr; decomposition with water

4. Cyclohexene, oxidized with OsO_4 or $KMnO_4$, gives *cis*-cyclohexene-1,2-diol, which on glycol cleavage with HIO_4 gives $O{=}CHCH_2CH_2CH_2CH{=}O$. This with $2\ CH_3MgI \longrightarrow$
$CH_3CH(OH)CH_2CH_2CH_2CH(OH)CH_3$.
Dehydration gives $CH_3CH{=}CHCH_2CH_2CH{=}CHCH_3$.

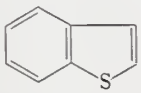
5. (*a*) $C_6H_5CH_2MgCl + CO_2$
(*b*) $C_6H_5CH_2Cl + Na^+C^-H(CO_2C_2H_5)_2 \longrightarrow$ $C_6H_5CH_2CH(CO_2C_2H_5)_2$, hydrolysis and decarboxylation
(*c*) $C_6H_5CH_2MgCl$ + ethylene oxide $\longrightarrow$ $C_6H_5CH_2CH_2CH_2OH$. This with PCl_3 gives the chloride, then: $C_6H_5CH_2CH_2CH_2MgCl + CO_2 \longrightarrow$ $C_6H_5CH_2CH_2CH_2CO_2H$.
(*d*) $C_6H_5MgBr + C_6H_5COCl \longrightarrow C_6H_5COC_6H_5$

6. (*a*) $C_6H_5COCH_2COC_2H_5$
(*b*) 2-Carbethoxycyclohexanone
(c)



(Parabanic acid)

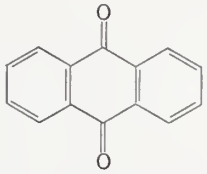
7. (a)



(Thionaphthene)

(*b*) No Friedel-Crafts reaction
(*c*) 1,3-Dimethylnaphthalene

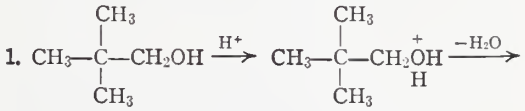
8.

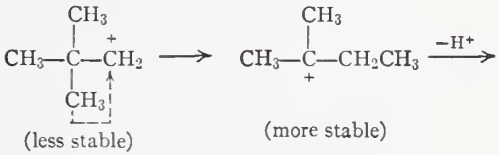


(Anthraquinone)

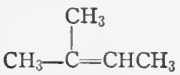
CHAPTER 14. REARRANGEMENTS

1.

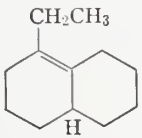




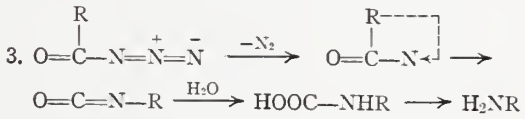
(less stable) (more stable)



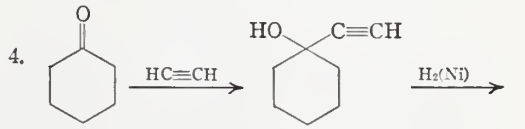
2. (*a*) With diazomethane
(*b*) With lithium aluminum hydride (12.15)
(*c*) The structure is analogous to that of neopentyl alcohol, and the alcohol would be expected to undergo Wagner-Meerwein rearrangement to:

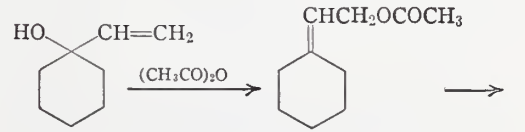


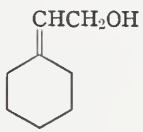
3.



4.





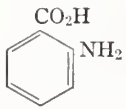


5. $CH_3C(=O)CHCOOC_2H_5$ with $OCH_2CH{=}CH_2$ (I) $\longrightarrow$ $CH_3C(=O)CHCOOC_2H_5$ with $CH_2CH{=}CH_2$ (II)

The reaction differs from the rearrangement of *o*-allylphenol only in that the initial keto-product II is more stable than the enol form.

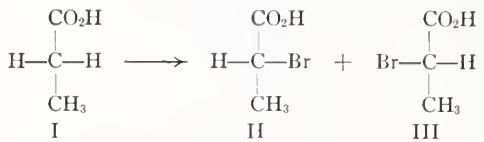
6. The products formed in the low- and high-temperatures are the 4-aceto ($COCH_3$) and 2-aceto derivatives.

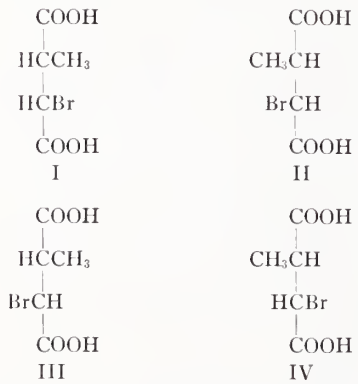
7. Yes. Fischer esterification reaches an equilibrium and some unesterified acid is inevitably present (see Answer 9.2); the reaction with diazomethane is irreversible.

8.  (Anthranilic acid)

CHAPTER 15. OPTICAL ISOMERISM

1. Since the two hydrogens in I are identical, there is exactly the same opportunity for replacement of one as of the other. Hence II and III, representing *d*- and *l*-forms, are formed in equal amount.



2. 

I is the enantiomer of II and is diastereoisomeric with III and IV; III and IV are enantiomers.

3. (*a*) 4; (*b*) 2; (*c*) 8; (*d*) 16

4. $CH_3CH_2CH(CH_3)COOH$

5. Monomethyl ester of mesotartaric acid

6. (*a*) *d*-, *l*-, *dl*-
(*b*) No stereoisomers
(*c*) *cis* and *trans*
(*d*) *d*-, *l*-, *dl*-
(*e*) *d*-, *l*-, *dl*-, *d'*-, *l'*-, *d'l'*-
(*f*) No stereoisomers
(*g*) *d*-, *l*-, *dl*-, *meso*-
(*h*) Eight optically active isomers; four *dl*-forms

7. Partial epimerization at the asymmetric carbon atom adjacent to the carbonyl group (through enol form).

8. It must be tetrahedral.

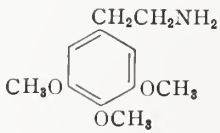
9. Since the two double bonds lie in planes perpendicular to each other, an allene with four different substituents should exhibit molecular asymmetry and hence be resolvable into optically active components. Even an allene of the type $R_1R_2C{=}C{=}CR_1R_2$ should be resolvable. Allenes are very reactive and very easily isomerized to acetylenes, and it was not until 1935 (Mills, England; Kohler, U.S.A.) that the predictions were verified.

10. Pairs (*a*), (*c*), and (*d*) are epimers. Pairs (*a*) and (*c*), but not (*d*), should be interconvertible through the common enols.

11. (*a*), Epimeric diastereoisomers, the first is optically active, the second inactive (*meso*); (*b*), identical; (*c*), structural isomers; (*d*), enantiomers, optically active; (*e*), diastereoisomers, optically active.

12. The fluorescent agent originally has the *trans*-configuration but on absorption of light it may change in part to the *cis*-form, which probably is less powerfully fluorescent.

13. The chemical evidence does not distinguish between the structure shown and the alternate structure



Mescaline

with the amino group at the α- rather than the β-position in the side chain, but a naturally occurring base of the latter structure would contain an asymmetric carbon atom and should be optically active. Synthesis: $(CH_3O)_3C_6H_2CHO + CH_3NO_2$ (OH^-, heat) $\longrightarrow$ $(CH_3O)_3C_6H_2CH{=}CHNO_2 \longrightarrow$ $(CH_3O)_3C_6H_2CH_2CH_2NH_2$.

CHAPTER 16. CARBOHYDRATES

1. A 2-ketopentose: $HOCH_2CHOHCHOHCOCH_2OH$

2. On oxidation with HNO_3 (*a*) would give a C_6-monoacid and (*b*) would give a C_6-diacid. Rhamnose gives a monoacid and therefore is (*a*).

3. On reaction with excess phenylhydrazine (*a*) would give a phenylhydrazone and (*b*) would give an osazone.

4. Isomer (*a*) would not react with phenylhydrazine until after it had been hydrolyzed with dilute acid and then it would give an osazone, (*b*) would react directly to give a methoxyl-containing phenylhydrazone;

isomer (*c*) would react directly to give a methoxyl-containing osazone.

5.





6. Galactose yields an inactive C_6-diacid, talose an active acid.

CHAPTER 17. LIPIDS

1. (*a*) Eight asymmetric carbon atoms, 256 possible forms
(*b*) Eleven asymmetric carbon atoms, 2048 possible forms

2. By extraction from an ethereal solution with alkali (estradiol is phenolic)

3. Vitamin D_3 has a conjugated triene system and absorbs ultraviolet light (λ_{max} 265 mμ); cholesterol (one double bond) shows no measurable absorption.

4. Zerewitinoff determination (11.4, liberation of two moles of CH_4 from CH_3MgI)

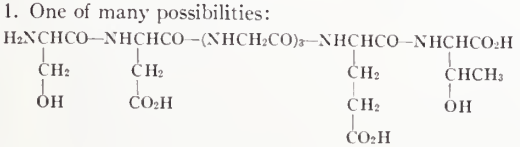
5. *trans*-Cyclohexane-1,2-diol

6. The conjugated triene system of the eleostearic acid groups of the tung oil glyceride would be evident from characteristic ultraviolet absorption bands. The glycerides of the unsaturated components of linseed and peanut or whale oil show no ultraviolet absorption.

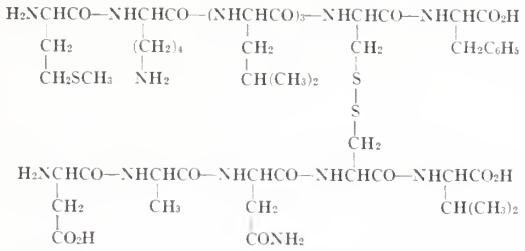
7. Reaction (*a*) gives a diphenyl carbinol, $-CH_2C(OH)(C_6H_5)_2$, which (*b*) is easily dehydrated to a diphenylethylene $-CH_2CH{=}C(C_6H_5)_2$; NBS effects allylic bromination at C_{22} (*c*); splitting out of HBr (*d*) gives a diene, $CH_3C(-){=}CHCH{=}C(C_6H_5)_2$; this is brominated by NBS (*e*) in the methyl group (activated by the diene system); $BrCH_2C(-){=}CHCH{=}C(C_6H_5)_2$; on reaction with CH_3COOK (*f*), halogen is replaced by the acetoxy group; a final step of oxidation (*g*) cleaves the 20,22-double bond and gives II.

CHAPTER 18. PROTEINS

1. One of many possibilities:



2.



3. Alanine is a dipolar ion, $CH_3CH(NH_3^+)COO^-$, whereas the derivative

$$2,4\text{-}(NO_2)_2C_6H_3NHCH(CH_3)COOH$$

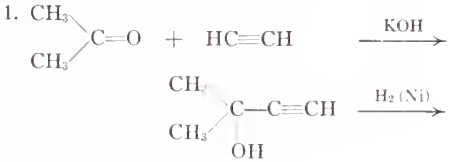
has the general character of a monocarboxylic acid, since the inherent basic character of the α-amino group is obliterated by the inductive effect of the aromatic ring containing two nitro groups. Furthermore, the molecular weight of the derivative is 166 units higher than that of alanine. Both factors increase the lipophilic character of the derivative and hence make the Rf value very much less than that of alanine.

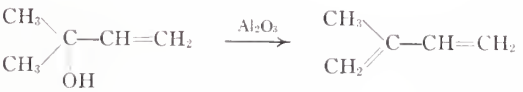
4. Met—Asp—Phe—Ser—Tyr

5. Gly—Ala—CySH—Glu—Met—Ala—Leu

CHAPTER 19. POLYMERS

1.





2. References to the methods are: 2,3-dimethylbutadiene-1,3, 10.3; butadiene, 5.2; acetylene, 8.18; chloroprene, 19.7; styrene, 6.22; acrylonitrile, 3.22.

3. See 3.4.

4. In cellulose, the two hydroxyls joined to the ring are equatorial, and the $-CH_2OH$ group is also equatorial. However, the ring hydroxyls are secondary, and CH_2OH is primary. Since secondary groups, due to hindrance, are less reactive than primary groups, the diacetate A must contain an abundance of free $-CH_2OH$ groups and diacetate B an abundance of $-CH_2OCOCH_3$ groups.

5. References to the methods are: ethylene and propylene, 8.10; vinyl acetate, 3.24; vinyl chloride, 10.11; methyl methacrylate, 19.24.

6. (*a*) Every monomer listed can be produced as a petrochemical.
(*b*) From acetylene: chloroprene, acrylonitrile, vinyl acetate.
(*c*) Dimerization of acetylene to vinylacetylene and selective hydrogenation.

CHAPTER 20. DYES

1. Naphthalene on high-temperature sulfonation yields naphthalene-β-sulfonic acid; fusion of the sodium sulfonate with alkali gives β-naphthol. Second component: $C_6H_6 \longrightarrow C_6H_5NO_2 \longrightarrow C_6H_5NH_2 \longrightarrow C_6H_5NH_3^+O^-SO_3H$; baking effects dehydration and conversion through orthanilic acid to sulfanilic acid, $p\text{-}H_2NC_6H_4SO_3H = p\text{-}H_3N^+C_6H_4SO_3^-$. Solution in Na_2CO_3 (as $H_2NC_6H_4SO_3^-Na^+$) + HCl + $NaNO_2 \longrightarrow N{\equiv}N^+C_6H_4SO_3^-$, which couples with β-naphthol in alkaline solution to give Orange II.

2. Electrolytic reduction of $C_6H_5NO_2$ gives

$$C_6H_5NH{-}NHC_6H_5$$

(hydrazobenzene), rearranged by acid to

$$p\text{-}NH_2C_6H_4C_6H_4NH_2\text{-}p'$$

(benzidine). Naphthalene $\longrightarrow$ α-nitronaphthalene $\longrightarrow$ α-naphthylamine; baking of the sulfonic acid effects dehydration and rearrangement to naphthionic acid.

3. (*a*) No; each of the two benzene rings of the molecule carries two carbonyl substituents and hence is strongly deactivated. One such group suffices to inhibit the Friedel-Crafts reaction.
(*b*) No; the α-position is *ortho* to one carbonyl group and the β-position is *para* to the other. Actually substitutions under forcing conditions give the α-nitro and the β-sulfonic acid derivatives.
(*c*) It is comparable to the nucleophilic displacement of chlorine in *o*- and *p*-nitrochlorobenzene (11.31).

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BOND DISTANCES (* DESIGNATES HYBRID BOND)

BOND	TYPE	DISTANCE, Å	BOND	TYPE	DISTANCE, Å
C—C	R—R	1.54	C—N	$(CH_3)_3N$	1.47
C—C	Ar—R	1.54	C—N	$CH_3—NO_2$	1.46
C—C	Cyclopropane	1.53	C—N*	Trinitrobenzene	1.4
C—C	$CH_3CH{=}CHCH_3$	1.54	C—N	$H_2N—CHRCO_2H$	1.47
C—C*	$CH_3C{\equiv}N$	1.49	C≡N	$HC{\equiv}N$	1.15
C—C*	$CH_3C{\equiv}CCH_3$	1.47	$C^{\cdots}\!\!-\!\overset{+}{N}$*	Diazomethane	1.34
C—C*	$C_6H_5—C_6H_5$	1.48			
C—C*	$CH_2{=}CH—CH{=}CH_2$ (2,3-bond)	1.46	$C^{\cdots}\!\!-\!\overset{+}{N}$*	Urea	1.37
			$C^{\cdots}\!\!-\!N$*	Pyridine	1.37
C—C*	Furan (β,β-bond)	1.46	C—S	CH_3SCH_3	1.82
C—C*	Thiophene (β,β-bond)	1.44	C=S*	CS_2	1.54
C—C*	O=CH—CH=O	1.47	C—F	CH_3F	1.42
C—C*	N≡C—C≡N	1.37	C—F	CCl_2F_2	1.35
C—C*	HC≡C—C≡CH	1.36	C—Cl	CH_3Cl	1.77
C=C	$R_2C{=}CR_2$	1.33	C—Cl	$(CH_3)_3CCl$	1.78
C=C	$CH_2{=}C{=}CH_2$	1.33	C—Cl*	$CH_2{=}CHCl$	1.69
$C^{\cdots}\!\!-\!C$*	Benzene	1.40	C—Cl*	C_6H_5Cl	1.70
$C^{\cdots}\!\!-\!C$*	Naphthalene	1.36, 1.39	C—Cl	$HC{\equiv}CCl$	1.68
C≡C	$RC{\equiv}CR$	1.20	C—Cl	$N{\equiv}CCl$	1.67
C≡C	$C_6H_5C{\equiv}CC_6H_5$	1.19	C—Br	CH_3Br	1.91
C—H	CH_4	1.09	C—Br*	$CH_2{=}CHBr$	1.86
C—H	$CH_2{=}CH_2$	1.09	C—I	CHI_3	2.12
C—H*	$HC{\equiv}CH$	1.06	C—I*	$CH_2{=}CHI$	2.03
C—H*	$HC{\equiv}N$	1.06	O—H	H_2O	0.96
C—O	CH_3OCH_3	1.42	N—H	NH_3	1.01
C—O	$CH_3—ONO_2$	1.43	N—O	$CH_3O—NO_2$	1.36
C—O	Dioxane	1.46	N—N	Calculated	1.40
C=O	$CH_2{=}O$	1.21	N=N	$C_6H_5N{=}NC_6H_5$ (*cis* and *trans*)	1.23
C=O*	CCl_3CHO	1.15			
C=O*	Carbon dioxide	1.16	$\overset{+}{N}{\equiv}N$*	Diazomethane	1.13
$C^{\cdots}\!\!-\!O^-$*	Carbonate ion	1.30	S—H	H_2S	1.35
$:C{=}\underset{\cdot\cdot}{O}:$*	Carbon monoxide	1.13	S—S	CH_3SSCH_3	2.04
C=O*	Carbon suboxide	1.20			

Bond Energies (kg.-cal./mole)

Bond	Energy	Bond	Energy	Bond	Energy
C—H	87.3	C—F	107.0	N—N	20.0
C—C	58.6	C—Cl	66.5	N≡N	170.0
C=C	100.0	C—Br	54.0	N—Cl	38.4
C≡C	123.0	C—I	45.5	S—H	87.5
C—O	70.0	H—H	103.4	S—S	63.8
C=O (CH_2O)	142.0	H-bond	5.0	F—F	63.5
C=O (RCHO)	149.0	H—F	147.5	Cl—Cl	57.8
C=O (R_2CO)	152.0	H—Cl	102.7	Br—Br	46.1
C—N	48.6	H—Br	87.3	I—I	36.2
C=N	94.0	H—I	71.4	Cl—F	86.4
C≡N (HCN)	144.0	O—H	110.2	Br—Cl	52.7
C≡N (RCN)	150.0	O—O	34.9	I—Cl	51.0
C—S	54.5	O=O	96.0	I—Br	42.9
C=S	103.0	N—H	83.7	Na—Na	18.5

Resonance Energies (kg.-cal./mole)

Compound	Energy	Compound	Energy
Acetamide	25	Furan	22.2
Acetic acid	25	Indole	54
Acetic anhydride	41	Naphthalene	75
Acetophenone	46	Phenanthrene	110
Aniline	45	Phenol	46
Anthracene	105	Phenylacetylene	49
Benzene	36	Pyridine	43
Butadiene-1,3	3.5	Pyrrole	24.5
Carbon dioxide	33	Quinoline	69
Crotonaldehyde	2.4	Stilbene	93
Cyclohexadiene-1,3	1.8	Styrene	46
Cyclopentadiene-1,3	2.9	Thiophene	27.7
2,3-Dimethylbutadiene-1,3	2.9	Toluene	39
Diphenyl	86[a]	1,3,5-Triphenylbenzene	64
Ethyl acetate	25	Urea	41

[a] 2 × 39 (benzene) + 8

Properties of Solvents

Solvent	Dielectric constant	Soly. in $H_2O^{20°}$, %	Solvent	Dielectric constant	Soly. in $H_2O^{20°}$, %
HCN (liq.)	95	∝	Pyridine	12.5	∝
Water	81.1		Aniline	7.2	3.49
Formic acid	47.9	∝	Acetic acid	7.1	∝
Nitromethane	39.4	sl. sol.	Ethylamine	6.3	∝
Acetonitrile	38.8	∝	Chlorobenzene	5.9	insol.
Nitrobenzene	36.1	0.19	Chloroform	5.0	0.82
Methanol	33.7	∝	Ether	4.3	7.5
Ethanol	25.7	∝	Triethylamine	3.1	$\propto < 19°$
Ammonia (liq.)	21	∝	Dioxane	2.3	∝
Acetone	21.4	∝	Benzene	2.3	0.06
Acetic anhydride	20.5	12	Carbon tetrachloride	2.2	0.1
n-Butanol	17.8	8.3	Pentane	1.8	insol.

Inductive Effects (aliphatic series)

Electron-attracting groups: $Cl > Br > I > OCH_3 > OH > C_6H_5 > CH{=}CH_2 > H$
Electron-releasing groups: $(CH_3)_3C > (CH_3)_2CH > CH_3CH_2 > CH_3 > H$

Electronegativity Values

F	4.0	S	2.5	B	2.0
O	3.5	C	2.5	Sn	1.7
N	3.0	I	2.4	Al	1.5
Cl	3.0	P	2.1	Mg	1.2
Br	2.8	H	2.1	Na	0.9